RELEVANCE OF SERUM BNP LEVEL IN THE STUDY OF HEART FAILURE WITH PRESERVED EJECTION FRACTION AT TERTIARY HOSPITAL

DISSERTATION

SUBMITTED TO

THE TAMIL NADU Dr. M.G.R MEDICAL UNIVERSITY

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF

MD GENERAL MEDICINE

Branch I

MAY 2019

DECLARATION

In the following pages is presented a consolidated report of the study **"RELEVANCE OF SERUM BNP LEVEL IN THE STUDY OF HEART FAILURE WITH PRESERVED EJECTION FRACTION AT TERTIARY HOSPITAL"**, on cases studied and followed up by me at Sree Mookambika Institute of Medical Sciences, Kulasekharam from 2016-2019. This thesis submitted to the Dr. M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulations for the award of MD Degree examination in General Medicine.

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CERTIFICATE BY THE GUIDE

This to certify that this dissertation entitled **"RELEVANCE OF SERUM BNP LEVEL IN THE STUDY OF HEART FAILURE WITH PRESERVED EJECTION FRACTION AT TERTIARY HOSPITAL"** is a bonafide research work done by **Dr Ankush Gupta,** under guidance and supervision in the Department of General Medicine during the period of his postgraduate study for **M.D. (General Medicine)** from 2016-2019.

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ACKNOWLEDGEMENT

First and foremost, I bow my head in reverence to The Almighty who gave me the strength, endurance and perseverance. I have always felt his presence in the form of my respected parents and teachers while sailing through the high and low challenges of my career, thus moving successfully towards my destination and serving the purpose dutifully that I am here for.

I extend my sincere heartfelt thanks to ***Dr. Velayuthan Nair****, Chairman and* ***Dr. Rema. V. Nair****, Director, for providing facilities to accomplish my dissertation work. I also thank the Principal of the Institution* ***Dr. Padmakumar*** *for his valuable support extended to me.*

I humbly wish to express my deep gratitude, whole hearted feeling of obligation and indebtness to Head of department of General Medicine and Guide ***Dr.Kaniraj Peter*** *for his guidance, encouragement and for his keen interest, invaluable suggestions and pain taking supervision throughout the period of this study.*

I humbly thank my Co-guide ***Dr. R. Ajay Kumar****, Chief Cardiologist whose support, guidance, help, critical views and comments throughout my study period was very enlightening. His suggestions were very valuable at each stage of my dissertation work. I am indebted to him for their guidance and support throughout my post graduate days.*

I am very much grateful to our Vice Principal and Academic Co-ordinator ***Dr. R.V.Mookambika*** *for her tremendous help, valuable support and guidance in carrying out the study. Her constant encouragement helped me to overcome obstacles during the study.*

I acknowledge my sincere thanks, respect and deepest gratitude to my teachers ***Dr.Krishanan kutty, Dr. Thilagar S, Dr. Mohandhas R*** *Dept. of General Medicine, Sree Mookambika Institute of Medical Sciences for their masterly advice, generous help and invaluable guidance throughout the course of this study.*

I extend my sincere gratitude to ***Dr. Beena Unnikrishnan, Dr. Robert Mathew, Dr.Sunitha Robert, Dr. Kiron Sukulal, Dr. Venkatesh Babu*** *for their innovative ideas.*

I wish to express my sincere thanks to ***Dr.Jayaram J.K,*** *Senior resident, for his help and valuable suggestions and all other staff members of General Medicine Department.*

Words are inadequate to express my sincere thanks and gratitude to my father ***Shri Ashok Kumar Gupta*** *for his kind blessings. He has been my driving force and inspiration in whatever I have accomplished today. I wish to thank my mother* ***Smt. Promila Gupta*** *for her unconditional love, unforgettable sacrifices, blessings and teachings. I thank my younger brother* ***Dr Himanshu Gupta*** *who offered invaluable support, love, encourgement and humour over the years.*

A special thanks goes to my colleagues ***Dr. Rishabh Gupta and Dr.Basavaraj S. Kumbar ,*** *who sailed the ups and downs of this journey with me and constantly supported me with a smile.*

My Sincere thanks to all my Supportive Seniors ***Dr. Jacob, Dr. Jineesh, Dr.Aswathi*** *and Juniors* ***Dr. Naveen, Dr. Shamini, Dr. Sona, Dr. DeviSree, Dr.Rijutha , Dr. Anand*** *who helped me to assemble the parts and gave suggestion about the task.*

I shall be failing in my duty if I do not express my thanks to all the patients who formed subjects of my study and were source of my learning.

“I thank the Almighty”

DR. ANKUSH GUPTA

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ABBREVIATIONS

ACEI	ACE inhibitors
AF	Atrial Fibrillation
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BSA	body Surface Area
CAD	Coronary Artery Disease
CBC	Complete Blood Count
cGMP	Cyclic Guano sine monophosphate
CHF	Congestive Heart Failure
CV	Cardiovascular
DD	Diastolic dysfunction
DF	Diastolic Function
DHF	Diastolic Heart Failure
DT	Deceleration Time
ECG	Electrocardiogram
ECM	Extra Cellular Matrix
EDP	End Diastolic Pressure
EDWS	End diastolic wall stress
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
ET	Exercise Training
FID	Functional Iron Deficiency
HF	Heart Failure
HFNEF	Heart Failure with Normal Ejection Fraction
HFPEF	Heart Failure with Preserved Ejection fraction
HFREF	Heart failure with Reduced Ejection Fraction
HR	Heart Rate
HTN	Hypertension
IVRT	Iso volumetric Relaxation Time

IVSTd	InterventricularSeptal Thickness Diastole
LA	Left Atrium
LFT	Liver Function Test
LV	Left Ventricle
LVEDP	Left Ventricle End Diastolic Pressure
LVEDP	Left Ventricular End Diastolic Pressure
LVEF	Left Ventricular Ejection Fraction
LVF	Left Ventricular Failure
LVH	Left ventricular Hypertrophy
LVIDd	Left ventricular Internal Diameter Diastole
LVIDs	Left Ventricular Internal Diameter Systole
LVMI	Left Ventricular Mass Index
NSAIDS	Non- Steroidal Anti-inflammatory drugs
NT-proBNP	N-terminal pro Brain type natriuretic Peptide
NYHA	New York Heart Association
OR	Odd Ratio
OSA	Obstructive Sleep Apnoea
PAH	Pulmonary Arterial Hypertension
PCWP	Pulmonary Capillary Wedge Pressure
PKG	Protein Kinase G
PSF	Preserved Systolic Function
PSVT	Paroxysmal Supraventricular tachycardia
RBS	Random Blood Sugar
RFT	Renal Function Test
SD	Standard deviation
SHF	Systolic Heart Failure
SR	Sinus rhythm
SVI	Stroke Volume Index
T2DM	Type 2Diabetes Mellitus

ABSTRACT

TITLE : "RELEVANCE OF SERUM BNP LEVEL IN THE STUDY OF HEART FAILURE WITH PRESERVED EJECTION FRACTION AT TERTIARY HOSPITAL"

INTRODUCTION : Heart failure with preserved ejection fraction (HFpEF) is becoming a more common diagnosis as the prevalence of patients with hypertension, diabetes and advancing age increases. HFpEF is now the cause of clinical heart failure in approximately 50% of patients, a frequent cause of hospitalization, and is associated with significant morbidity and mortality. In addition to clinical assessment, the severity of heart failure is assessed by measuring B-type natriuretic peptide (BNP), a peptide hormone released by cardiomyocytes in response to increased wall stress in patients of HFPEF". It is planned to study all such cases of HFpEF (diagnosed with ECHO) and relevance of raised brain type natriuretic peptide (BNP) levels with that.

OBJECTIVE : **"**To study the relevance of serum B type Natriuretic peptide levels in patients presenting with acute left heart failure with preserved ejection fraction".

METHODS: 50 patients presenting in Emergency Department (ED) or Inpatient Department (IPD) and Intensive care unit (ICU) with diagnosis of Diastolic dysfunction were taken in this study. Detailed 2D Echo, BNP levels along with routine blood samples were taken. The study took place for a period of 18 months. Statistical analysis was done using Percentage, Standard error of proportion and chi-square test.

RESULTS: In present study 50 HFPEF patients were taken whose mean age group was 63.60 years and majority of the patients were female (62%) and were overweight with mean BMI of 25.24 Kg/m^2 and had associated comorbidities in the form of hypertension (68%), diabetes mellitus (62%). In the present study, BNP levels were higher in majority of the patients with significant association to all the parameters like age, sex, comorbidities, LA size (p - 0.001), Diastolic Dysfunction type (p – 0.033) and NYHA grade.

CONCLUSION: The present study of 50 cases of HFPEF was aimed at highlighting BNP relevance in HFPEF patients with in terms of age & sex distribution, vital parameters, laboratory parameters, comorbities, M- mode echocardiography, NYHA class, Diastolic dysfunction type at the time of presentation. Thus, focus should be on monitoring diastolic disease progression in the preclinical phase and prevention of heart failure hospitalization. Thus, studies should be done to identify patients who may benefit from closer surveillance and tighter control of their risk factors.

INTRODUCTION

Heart Failure is defined as a syndrome characterized by an impaired ability of the heart to fill with and/or to eject blood commensurate with the metabolic needs of the body, resulting in a classic constellation of signs or symptoms of pulmonary and systemic venous congestion.[1]

Heart failure is defined as a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood, which in turn leads to the cardinal symptoms of dyspnea and fatigue and signs of HF, namely edema and rales.[2] Heart failure (HF) affects about 2% of the western population, with the prevalence increasing sharply from 1% in 40-year-old individuals to 10% above the age of 75 years. It is the most common cause of hospitalization in patients over 65 years of age.[1,3,4] It is a debilitating condition with frequent hospitalization with a very high mortality rate with economic and public health burden. Heart failure once thought to arise primarily in the setting of depressed left ventricular (LV) ejection fraction (EF). However, epidemiologic studies have shown that approximately one-half of the patients who develop heart failure (HF) have a normal or preserved ejection fraction (EF>50%).[5]

Heart failure with preserved ejection fraction (HFpEF) is becoming a more common diagnosis as the prevalence of patients with hypertension, diabetes, chronic kidney disease (CKD) and advancing age increases. HFpEF is now the cause of clinical heart failure in approximately 50% of patients, is a frequent cause of hospitalization, and is associated with significant morbidity and mortality. The diagnosis of HFpEF depends on the clinical diagnosis of heart failure in the setting of

preserved ejection fraction, usually with an ejection fraction 45%.[6] In addition to clinical assessment, the severity of heart failure is often assessed by measuring B-type natriuretic peptide (BNP), a peptide hormone released by cardiomyocytes in response to increased wall stress.[7]

The most useful and gold standard method for diagnosing heart failure is echocardiography. The main disadvantages of echocardiography are

- In patients who are obese and have concomitant chronic lung disease with respiratory distress echocardiography is ineffective.
- It is more difficult to diagnose heart failure in patients who are having normal ejection fraction .

Because of these disadvantages biochemical markers are used for accurate diagnosis and prognosis of heart failure by clearly determining its incidence and stage.[8] B-type natriuretic peptide (BNP)is the most commonly used laboratory test because its clinical usefulness in diagnosis and prognostic rating of heart failure is proven in large number of studies.[9,10] To address this problem, this paper focuses on the significance of BNP in patients with heart failure.

BNP is a substance secreted from the ventricles or lower chambers of the heart in response to changes in pressure that occur when heart failure develops and worsens. The level of BNP in the blood increases when heart failure symptoms worsen, and decreases when the heart failure condition is stable. The BNP level in a person with heart failure even someone whose condition is stable is higher than in a person with normal heart function.[11] Signs or symptoms of congestive heart failure include lung crepitations, pulmonary oedema, ankle swelling, hepatomegaly,

dyspnoea on exertion, and fatigue. Different modes of presentation of dyspnea (i.e. effort related or nocturnal) need to be distinguished.[12] In HFNEF, breathlessness is frequently the earliest symptom due to pulmonary congestion.[13]

The management of heart failure with diastolic dysfunction is not well defined than the management of heart failure with systolic dysfunction and remains a challenge. Hence the need for study. It is planned to study all such cases of HFpEF (diagnosed with ECHO) and relevance of raised brain type natriuretic peptide (BNP) levels with that. This study is likely to make available a variety of information (especially ECHO and clinical data) that should better characterize the syndrome of diastolic dysfunction and hopefully provide directions and to plan its better management.

AIMS AND OBJECTIVES

The aim of the present study was as follows:-

- To study the relevance of serum B type Natriuretic peptide levels in patients presenting with acute left heart failure with preserved ejection fraction.

REVIEW OF LITERATURE

Diastole means 'expansion' in Greek and includes the part of the cardiac cycle starting at the closure of AV valve, when the pressure in LV falls below aortic pressure and finishing at the closure of mitral valve. A normal LV diastolic dysfunction may be clinically defined as the capacity of the left ventricle to receive a LV filling volume able in its turn to guarantee an adequate stroke volume, operating at a low pressure regimen. Diastole or relaxation is the process whereby the myocardium returns after contraction to its unstressed length and force. It related to the processes underlying ca^{2+} extrusion from the cytosol and cross bridge detachment. As a vitality expending process, anomalous LV active relaxation is either due to cardiac ischemia or abnormalities in myocardial energy metabolism.[14]

Diastole is a complex process which is influenced by various factors such as ischemia, heart rate, velocity of relaxation, cardiovascular consistency, left ventricular hypertrophy and segmental wall coordination of the heart muscle. The term diastolic dysfunction refers to abnormal mechanical (diastolic) properties of the left ventricle. It demonstrates abnormal distensibility of diastole, filling or LV relaxation/ compliance and increased LV passive stiffness that alters the ease with which blood flows despite of whether the EF is preserved or abnormal or whether the patient is symptomatic or asymptomatic.

When diastolic dysfunction becomes symptomatic i.e. when dyspnoea occurs - diastolic heart failure occurs. Diastolic dysfunction may be present several years before any symptoms occur and may represent the first phase of diastolic heart failure. Asymptomatic diastolic dysfunction manifested by severe LVH and/or abnormal echo

parameters is frequently found in hypertension and ischemic heart disease. Although many such patients remain asymptomatic for some time, there is a clear relationship between diastolic functional abnormalities and long term hospital admissions for HF. Patients of HFPEF are characterized more often with a non dilated LV, concentrated LVH or atleast concentric LVH remodelling and normal LVEF. A comparison of endomyocardial biopsies revealed higher cardiomyocytes diameter and higher myofibrillar density in patients with HFPEF compare with those with HF and impaired LVEF. [15]

HFPEF has impaired DD due to concentric remodelling of the heart along with impaired LV compliance and with increased substrate of LV stiffness which is due to deposition of type 1 collagen which results in a stiff and noncompliant ECM.[16] Now recent, studies are being focusing on oxidative stress, inflammation endothelial dysfunction along with molecular cell level disorder that impairs nitric oxide- cyclic guanosine monophosphate (cGMP) -protein kinase G (PKG) signaling pathways which are thought to have a role in patients with HFPEF. [17]

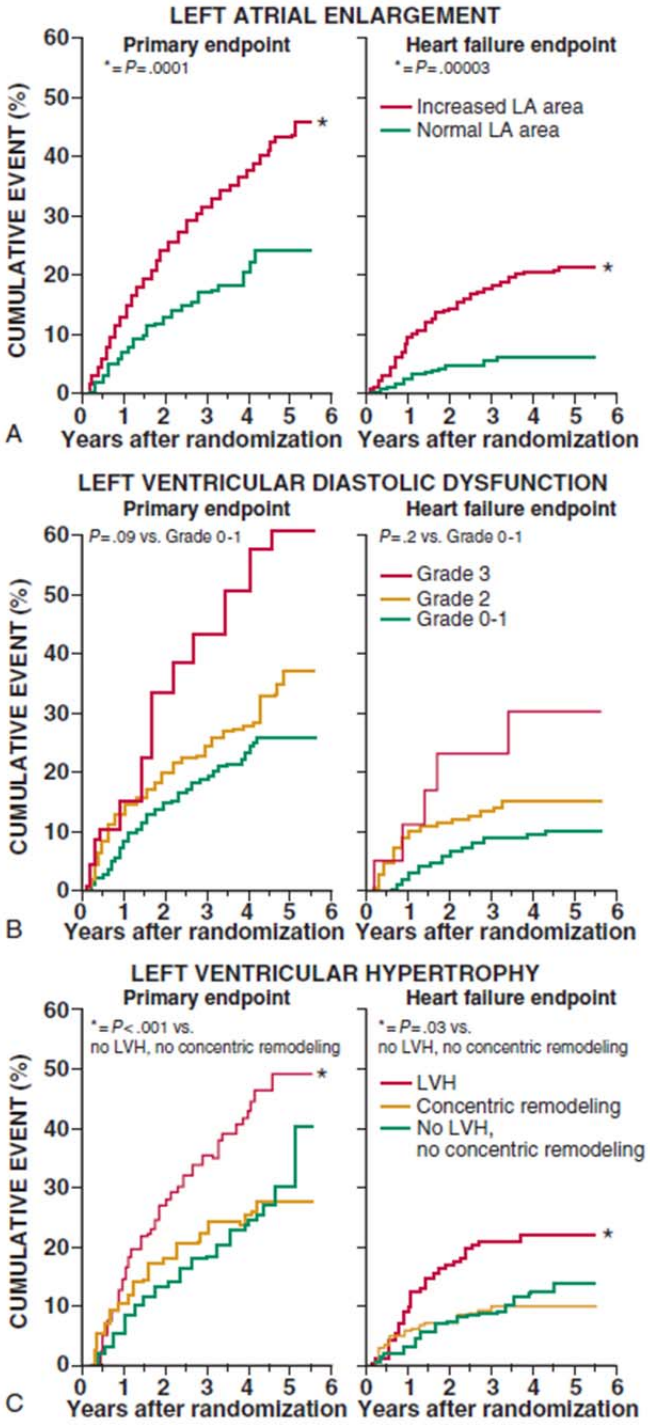


FIG: 1 Prognostic importance of changes in cardiac structure and function in patients with HFpEF. A- Left atrial enlargement, B -Diastolic Dysfunction type, C - LV hypertrophy [18]

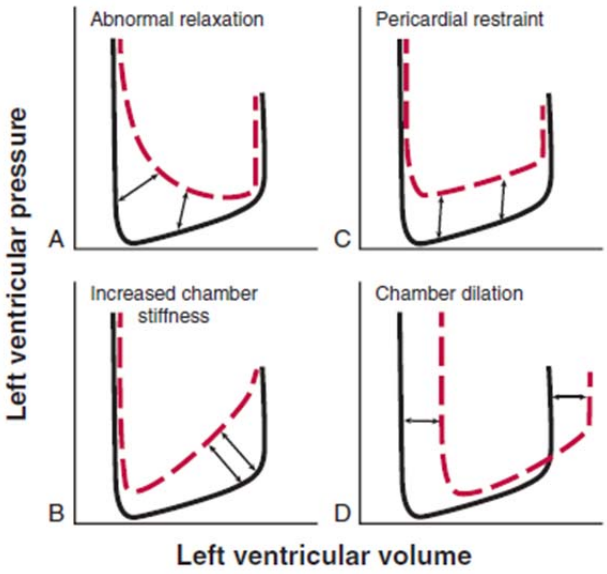


FIG: 2 Mechanisms of increased LV diastolic pressure.

There are 4 patterns of DPVR (Diastolic pressure volume relationship) can be found out in patients with heart failure and increased LV diastolic pressure.

DPVR in patients with HFpEF may be described by graphed curves A to C.

In curve A, the relaxation is prolonged and LV diastolic pressure reduced throughout diastolic but remains increased.

Curve B is the most prevelant pattern in HFPEF and in this DPVR shifting upwards and to left, indicating reduced distensibility, where LV pressure is increased at any LV volume.

In curve C, there is an upward parallel shift in DPVR due to pericardial constraint.

Curve D indicated DPVR in patients with HFrEF. In that curve there is eccentric remodeling which leads to right side shift of DPVR due to increased distensibility. It is clear that even the ventricle is distensible, there is high end diastolic volume and also end-diastolic stiffness is high.[19]

ETIOLOGY OF PRESERVED EJECTION FRACTION(>40-50%) [20]

1. **Pathologic Hypertrophy-**

   - Primary (Hypertrophic Cardiomyopathies)
   - Secondary (Hypertension)
   - Aging

2. **Restrictive Cardiomyopathy**

   - Infiltrative disorders (Amyloidosis, Sarcoidosis)
   - Storages diseases (haemochromotasosis)
   - Fibrosis
   - Endomyocardial disorders

Hypertension, Diabetes and Cardiac ischemia are the most common causes of Heart Failure with Normal ejection Fraction. [21]

Prevalence of hypertension : 83% approximately

Prevalence of Diabetes : 30% approximately

Prevalence of CAD : 40 - 50% approximately

Impairment of diastolic dysfunction appears to be age related and multiple studies have shown that 10% of patients with HF below the age of 50 years have diastolic dysfunction and this rises up to 70% in patients aged over 80 years. [22] Diastolic dysfunction has been shown to affect geriatric women more than any other population subgroup.

Consistent with the burden associated with HFPEF, the prognosis of patients with HFPEF also appears to be marginally better than that of HFREF. Recent studies showed that deaths which are not related to cardiac causes are higher in patients with HFPEF as compared to patients with HFREF, and it could be a due to the multiple complicity of the diseases in patients with HFPEF.[23]

Data is very limited regarding the heart failure prevalence and incidence depending upon the EF and how it had changed over time. In cross-sectional studies, the proportion of patients with preserved ejection fraction ranges from 40-70% with an average of about 50%.[24] Doppler echocardiography and tissue Doppler echocardiographic techniques show that almost 30-50% patients with symptomatic HF have a relatively normal or preserved ejection fraction but are associated with abnormalities of compliance, stiffness and relaxation. The mortality rate of heart failure with diastolic dysfunction is as high as that of systolic dysfunction. Reported annual mortality rates for patients with diastolic dysfunction vary from 5.2% to 17.5% compared with 15-20% for patients with systolic dysfunction. [25]

The prevalence of HFPEF has shown an increment in the last 15 years but mortality remains unchanged by this disorder. These patterns underscore the significance of this developing general medical issue and the pressing need to characterize particular treatment for this element. [24]

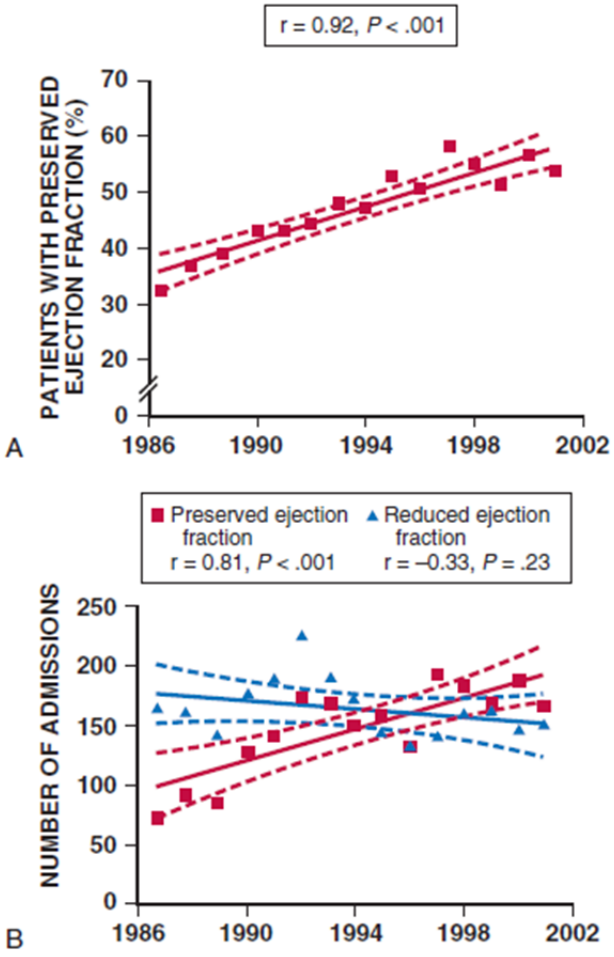


FIG :3 Prevalence of heart failure–related hospital admissions in patients with HFpEF.

A, From 1987 to 2001,the number of patients with HFPEF form of heart failure is increased indicating that its prevalence continues to increase. This graph shows the percentage of number of patients with HFPEF form of heart failure.

B, In this same 15-year , there is stable/ slightly downward trend in hospitalizations of patients with HFrEF but HFpEF patients, the number increasing significantly.[26]

Diastolic dysfunction on the basis of history, clinical examination, ECG, chest radiographic findings is difficult to differentiate it from systolic dysfunction. Therefore, objective diagnostic testing with cardiac catheterization, Doppler echocardiography, and possibly measurement of serum levels of B-type natriuretic peptide is often required. Worsening stages of DD on 2Decho are associated with increased risk of adverse outcomes such as development of clinical HF. [27] BNP and NT-proBNP levels were found to be closely related to the severity of diastolic dysfunction. [28]

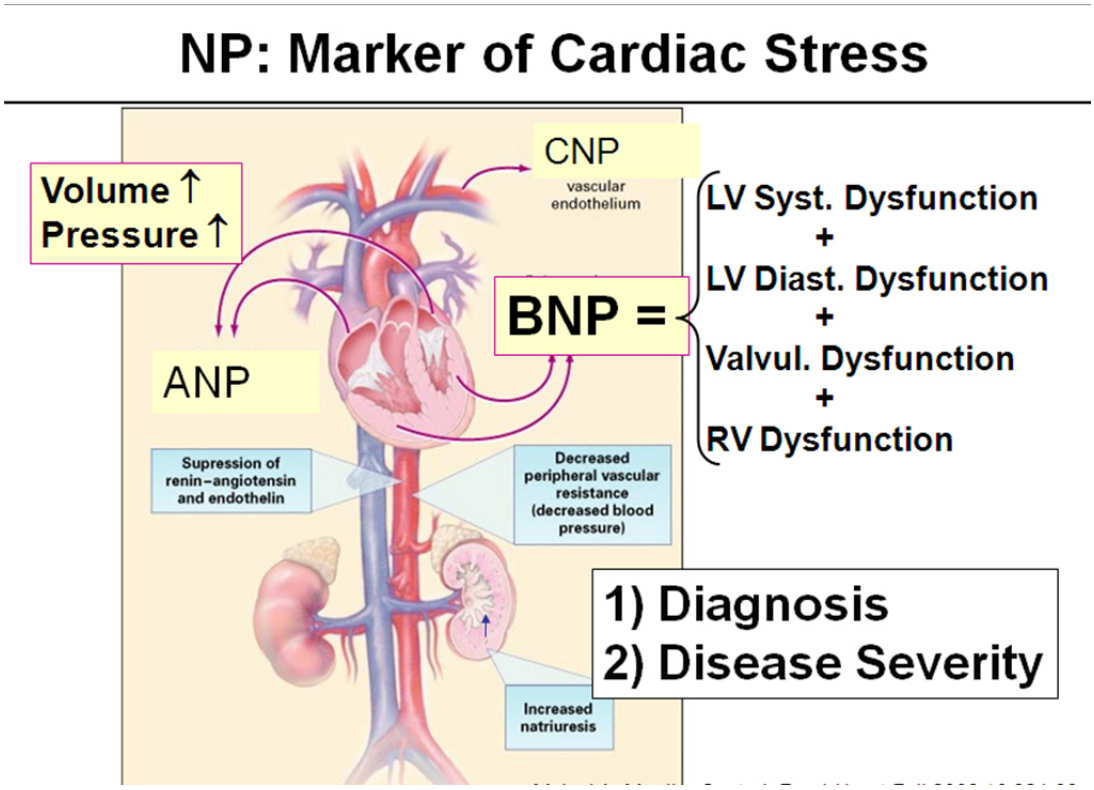


FIG 4: VARIOUS MARKERS OF CARDIAC STRESS

In response to changes in the pressure as in heart failure, Brain Type Natriuretic Peptides is secreted from the ventricles which is a polypeptide. BNP level is directly proportional to severity of heart failure. As the heart failure sympotoms

worsens BNP level increases and it decreases when the condition is stable . So BNP is used for the assessment of severity of heart failure.

BNP is a 134-amino acid preprohormone (preproBNP). It is encoded by the gene NPPB. Removal of the 25-residue N-terminal signal peptide produces the prohormone, proBNP, which is an O-linked glycoprotein and is stored intracellularly. With the help of a specific convertase (probably furin or corin) ProBNP is cleaved between arginine-102 and serine-103 into NT-proBNP and the biologically active 32-amino acid polypeptide BNP-32.They are secreted into the blood in equal amounts.[29] Cleavage at sites other than this produces shorter BNP peptides with unknown biological activity.[30] Processing of proBNP may be regulated by O-glycosylation of residues near the cleavage sites.[31]

BNP was first discovered in the porcine brain that's why it is named as brain natriuretic peptide. Later, it was discovered that in response to hemodynamic stimuli like ventricular volume expansion and pressure overload BNP is secreted from left ventricular myocardium. [32] BNP is cleaved into biologically active BNP C- terminal and the biologically inactive, NT-proBNP.

Then pro BNP enters into the circulatory system. ProBNP is the better diagnostic tool for ventricular dysfunction because it is secreted from the ventricles due to ventricular hemodynamic changes. [33] BNP causes :

- Strong vascular relaxation
- Natriuresis.

BNP does not causes changes in normal heart, but atrial natriuretic peptide (ANP) will cause changes. This is due to the increased production and secretion of

BNP in response to increased hemodynamic changes.[34] Neurohormonal theory explains main mechanism of heart failure; in view of this theory, BNP level increases because of the activation of natriuretic peptide system. This system acts as a counter-regulatory system and it counteract the impaired neurohormonal balance in response to activation of the systems that induce vascular spasms (sympathetic nervous system, endothelin system and renin-angiotensin system,). Therefore, BNP is reported to indicate ventricular dysfunctions more efficiently than other NPs.[35]

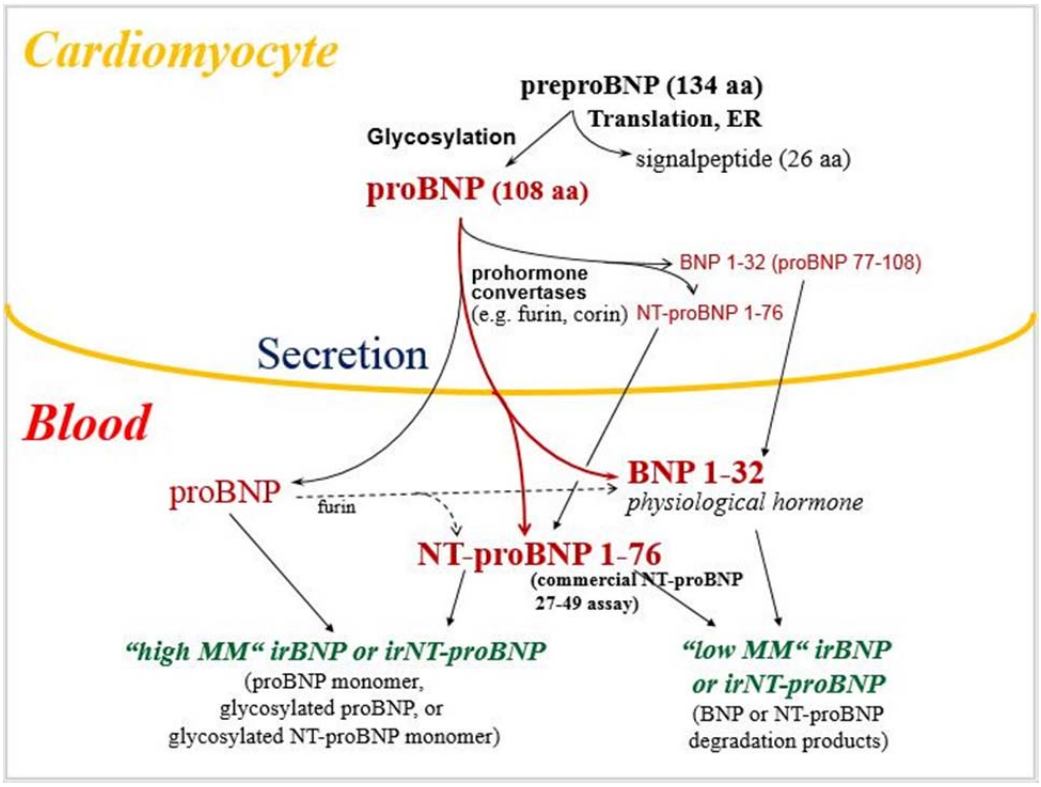


FIG : 5 MECHANISM OF FORMATION OF BNP

Physiological effects of BNP:

- Diuresis
- Natriuresis
- Vasodilator effects of the renin–angiotensin– aldosterone system (RAAS)

- Inhibition of the the sympathetic nervous system (SNS)
- Vasodilation[36]

Functions of NP system:

- In CVS- control of homeostasis and its functions via co-ordinated central and peripheral actions.
- In Brain stem- NPs decrease the sympathetic tone
- In the Hypothalamus -they decrease the secretion of arginine vasopressin and corticotropin;
- In areas adjacent to the Third ventricle -NP system inhibit salt appetite and water drinking.[37]

Now it is found that cardiovascular NPs plays an autocrine and paracrine role in the control of myocardial and vascular structure and function as well.

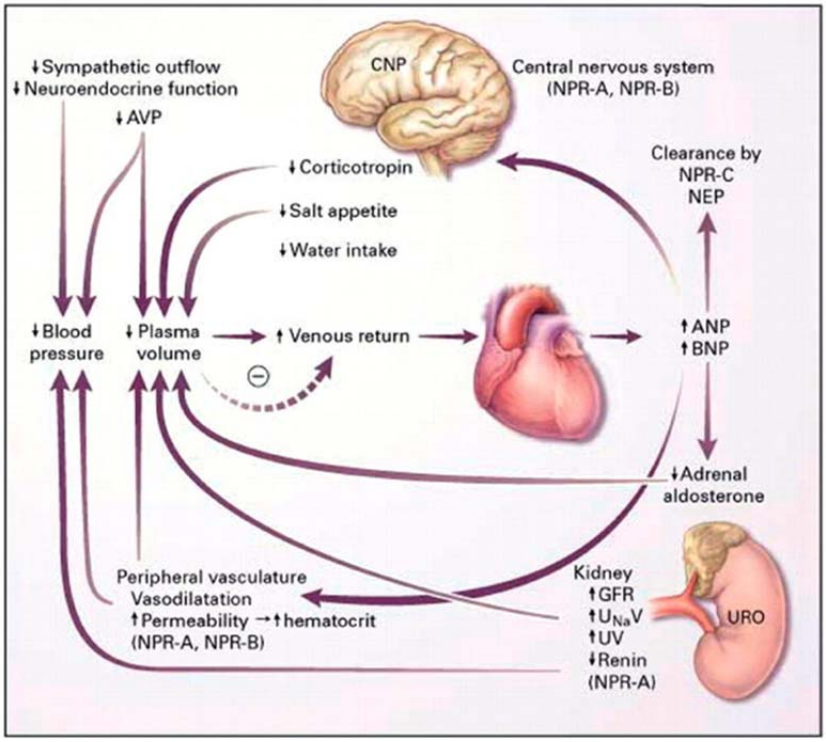


FIG : 6 EFFECTS OF BNP ON VARIOUS ORGANS

In the systemic circulation BNP causes intracellular cGMP production with the help of natriuretic peptide receptor type A (NPR-A).

Through proteolysis by neutral endopeptidases and by binding to the natriuretic peptide receptor type C (NPR-C) BNP is removed from plasma. But NT-proBNP is mainly removed by renal excretion. NT pro BNP serum values are 6 times higher than BNP this is because of the difference in the half lives. Half-life of BNP is 20 mins and NT-proBNP is 120 mins. Even though both molecules are released in equal proportion the difference in the half life are the reason for difference in serum levels.[38]

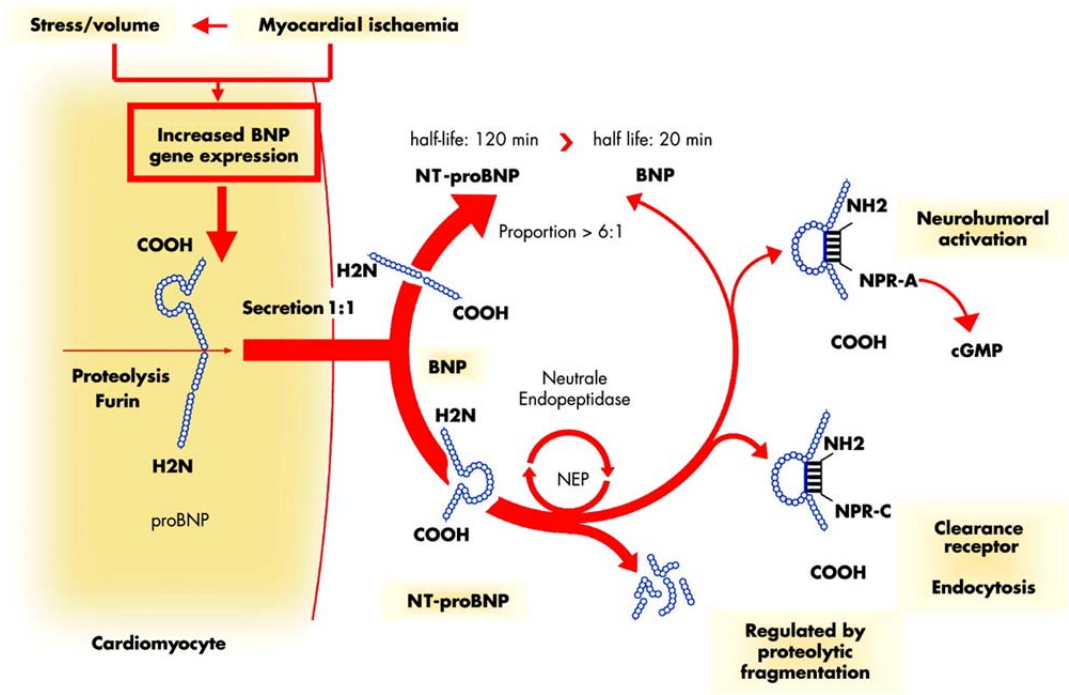


FIG : 7 B-type natriuretic peptide (BNP) synthesis, release and receptor interaction. In cardiomyocytes BNP is produced as a prohormone. After the release into the circulation proBNP is divided into BNP and the N-terminal fragment (NT-proBNP) in equal proportions. Increase in the intracellular cGMP level is due to the association of BNP and the natriuretic peptide receptor type A (NPR-A).

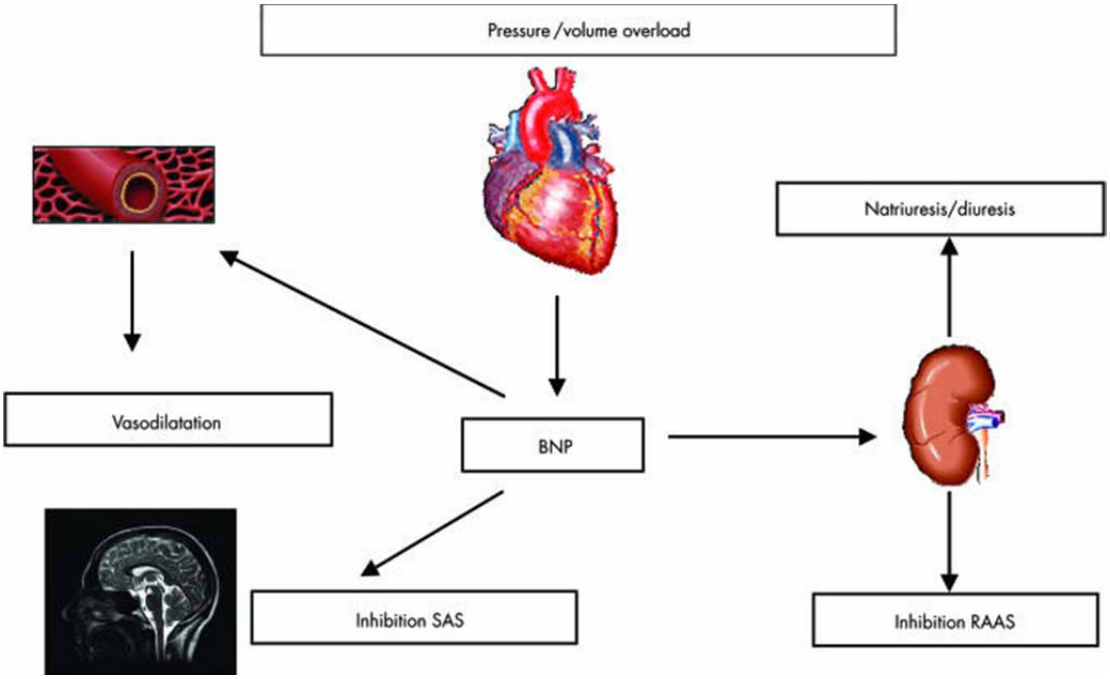


FIG : 8 - Physiological effects of B-type natriuretic peptide (BNP) and ventricular wall stress and BNP release is due to the volume or pressure overload.[38]

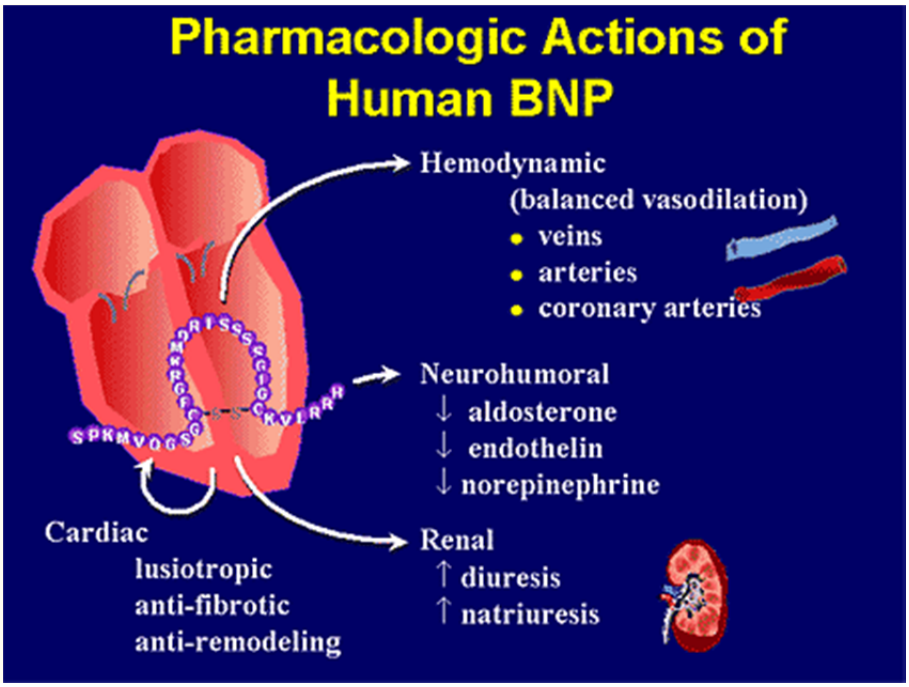


FIG : 9 - PHARMACOLOGIC ACTIONS OF BNP

BNP level is associated with severity of heart failure. In New York Heart Association functional classification the relation between BNP and heart failure

severity is clearly categorized. So BNP is an useful tool for predicting patients prognosis[39] .The criterion for the diagnostic value of a diagnostic test is its predictive power, which plays a crucial role in the process of therapeutic decision-making. BNP is an independent factor for the prediction of incidence and mortality rates.[40] BNP is believed as an important prognostic factor that should be considered in future clinical trials. [41]

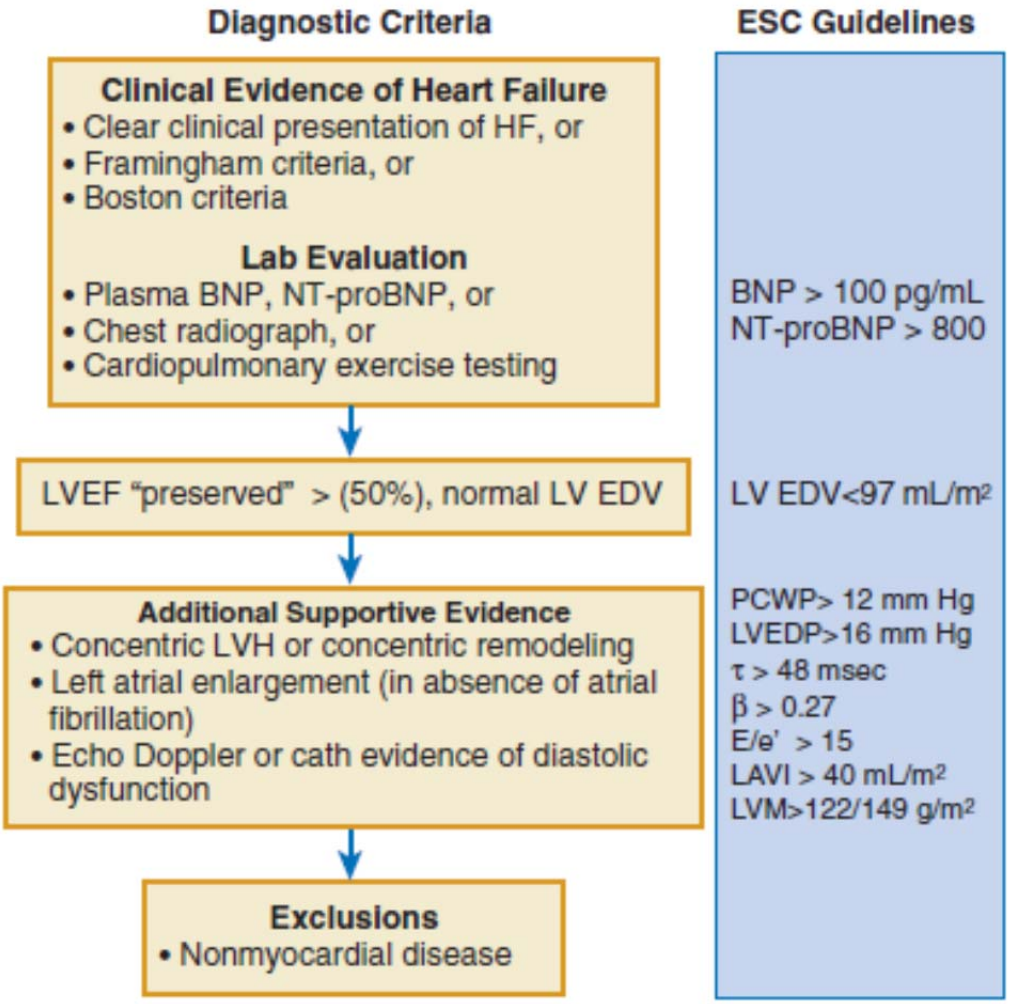


FIG : 10 DIAGNOSTIC CRITERIA FOR HFpEF from the Heart Failure Society of America.[42]

HFPEF rises with age and commonly affects those older than 70 years. [43] A review of the ADHERE database[44] has shown that, patients with HFPEF are elderly age group, female preponderance, and were hypertensive but less likely to have had a MI as compared to patients with systolic dysfunction. Other parameters were also studied in the form of various comorbid conditions and are also common which include obesity, CAD, DM, hyperlipidaemia and AF, which were same in comparison to patients with HFREF.[45] These all additive changes in cardiovascular structure and function along with a normal human ageing process increases risk for the development of this type of HFPEF. [46-47] First among these are changes or alterations in the stiffness of the central conduit artery along with increase in the hypertrophy of the left ventricular, and there is shift toward dependence on filling of left ventricle by left atrium (LA), and resulting in progressive enlargement of LA. The changes related to ageing along with development of changes in the endocrine, renal, pulmonary, ANS (autonomic nervous system) [48-50] causes changes in salt and water handling capacity of the body and resulting in increased vulnerability to acute pulmonary oedema because of altered pulmonary capacitance along with change in the distribution of blood volume.

European Society of Cardiology [51] in 2007 proposed a diagnostic criteria and said that haemodynamic and echocardiographic findings are key components for the diagnosing the patients of HFPEF. Firstly, Patients should have signs and symptoms for heart failure which is identified on the basis of Framingham criteria. Secondly, absence of depressed EF i.e. EF should be at least 50% in a non-dilated heart with a LVED volume of 97 mL/m2. Thirdly, objective measurements which are showing the presence of Left ventricular DD, that can either be demonstrated with Doppler echocardiography or with cardiac catheterization or by a biomarker i.e. BNP levels. In

spite of the fact that these criteria have expanded the specificity for which the conclusion of HFPEF is influenced, these criteria have been condemned. For instance, no information exists on the positive and negative predictive value of BNP and furthermore, in certainty few patients who are well compensated despite obvious symptoms of HF might not have increase in BNP levels[52]. Furthermore, in the Framingham Heart Study and Mayo clinic , it identified that BNP levels fluctuates according to sex and age of the patients so normal age- related and sex-related references value should be there before interpreting the BNP levels and making a diagnosis of HFPEF correctly.[53]

Invasive measurement of LV filling pressures always remains the gold standard investigation technique for the diagnosis of HFPEF and ought to be considered in cases in which diagnosis is questioned. Cardiac catheterization is additionally valuable for diagnosing pulmonary hypertension, which is commonly seen in patients of heart failure with preserved ejection fraction (HFPEF) and might be related to both post capillary pulmonary venous hypertension [54-55] as well as pre-capillary component of PAH.[56] A recent area of interest is a decrease in the longitudinal component of LV systolic function (easier to measure by 2D echo).[57] The lessening in the longitudinal part of LV systolic function is being compensated by a preserved circumferential, radial, and twist components that are important in helping a normal left ventricular ejection fraction.[58-59] Regardless of whether this can help in identifying cases of HFPEF needs larger prospective trials and studies which are suspected of this entity. So non-intervention things like haemodynamic assessment, echocardiographic evaluation is to be done in patients who are suspected with HFPEF. Plasma biomarker estimation i.e. Brain natriuretic peptides levels may help in diagnosis but in doubtful cases, the need of invasive assessment ought to be

considered to make the diagnosis. Tissue Doppler imaging is a more up to the date system that can be utilized with transmitral Doppler in combination to decide the presence and severity of this type of heart failure with diastolic dysfunction.

The most important indicator of diastolic function is to estimate the mitral inflow signal. By determining this signal we can assess the grade of diastolic dysfunction and also seen the individual pressure difference of atria and ventricles. This will help to assess any diastolic pressure difference in the chambers. This is assessed by checking any change in shape and velocity of the inflow Doppler signal. The most specific alteration seen is by checking the diastolic dysfunction during early and late filling time along with checking the rapidity of fall in velocity in early diastolic (E- wave) and the time taken for ventricles to get filled after relaxation (IVRT).

Grading of diastolic dysfunction can be represented as follows [60]

Grade I = the pattern of relaxation is impaired with normal filling pressure/elevated filling pressure

Grade II = Pseudo normalized pattern

Grade III = Reversible restrictive pattern

Grade IV = Irreversible restrictive pattern

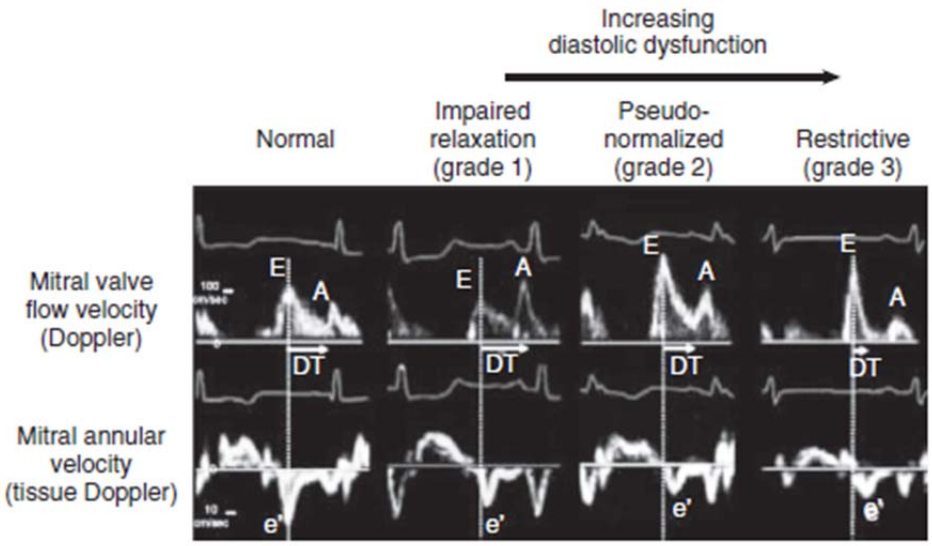


FIG : 11 - Evaluation of diastolic function is depend upon the left ventricular filling dynamics.

This is determined by Doppler measurement of mitral valve flow velocity and tissue Doppler measurement of mitral annular velocity. In general early diastolic mitral flow velocity (E) and the mitral annular velocity (e′) are brisk and occur nearly simultaneously. The mitral E velocity is reduced with mild diastolic dysfunction (impaired relaxation pattern—grade 1) and is less than the late diastolic mitral flow velocity (A). The E deceleration time (DT) is increased. In severe diastolic dysfunction (grades 2 and 3), E is increased and the DT is reduced. In these condition, e′ is reduced and delayed relative to the mitral E.[61]

In normal young subjects, Left ventricle elastic recoil is vigorous because of normal myocardial relaxation; so most of the filling is completed in early diastole. So, the E wave will be taller than A wave and the E/A ratio is usually 1.5 or higher, DT is 160 to 240 milliseconds, E/e' is less than 8. This vigorous relaxation can also be seen as active motion of the mitral annulus away from the apex during early diastole in

parasternal long- axis and apical four- chamber view. Filling does not start as soon as the systole ends. First in the ventricles pressure had to fall below the left atrial pressure and the time this happens is known as isovolumetric relaxation (IVRT) and is in between 50 milliseconds to 100 milliseconds. With normal myocardial relaxation, the longitudinal mitral annulus diastolic velocity pattern mirrors that of normal mitral inflow: early diastolic velocity (e′) is higher than late diastolic velocity (a′). Lateral annulus velocity is always higher (normal, >15 cm/sec) than septal e′. Thus e' increases with exercise in healthy subjects so that E/e′ is similar at rest and with exercise (usually <8). So as the age increases there is fall in rate of myocardial relaxation and elastic recoil of left ventricle and the pressure in the left ventricles started declining and filling becomes slower producing a diastolic function pattern as that of diastolic dysfunction grade I. At about 65 years of age the E wave velocity approaches A velocity and at around 70 years of age group it is < 1.

FIG : 12 - Normal pattern of diastolic filling: A-wave smaller than E-wave

GRADE I DIASTOLIC DYSFUNCTION (mild dysfunction) - Impaired relaxation with normal filling pressure.

An abnormal relaxation of the ventricle will impair early diastolic filling and the height of the E-wave will decrease and the pressure of atrium has to be high

enough to initiate filling. Thus, IVRT will rise to > 100 milliseconds, and the Deceleration Time will also be prolonged to ≥ 240 milliseconds. As less volume is moving into the LV during early filling stage so more blood will be accumulating in the later stages of atrial contraction so atrium has to conduct more blood and will take more time. A-wave will be larger than normal and will also be larger than the E-wave (E/A ratio < 1) and this impaired relaxation is known as diastolic dysfunction grade I.

FIG : 13 - Disturbed relaxation: the A-wave is larger than the E-wave

GRADE 2 DIASTOLIC DYSFUNCTION- Pseudo normal filling pattern/ Moderate DD

Progressive DD will further lead to increase in left atrial pressure. And increased atrial pressure further raises the pressure gradient of the atrium and ventricle of the left side and there will be increase in force to fill the ventricle during early diastole. Thus the size of the E-wave in relation to that of A-wave will increase, and E/A ratio will again return in normal range type that is in between 1 to 1.5 millisecond and normal Deceleration time and IVRT and this picture will look very similar to that of "normal" diastolic function. That's why this grading is also known as "pseudo normal" pattern and is known as grade II diastolic dysfunction. This pattern can be distinguished from normal one by performing Valsalva manoeuvre, by flow propagation time, e' ratio and many more methods.

FIG :14 - Pseudo normal filling: the E-wave is larger than the A-wave

GRADE 3 DIASTOLIC DYSFUNCTION- Reversible restrictive filling pattern

In this , increase in the further filling pressure will raise the pressure difference between left sided atrium and ventricles will further increase in the E wave with subsequent shortening of A wave. So the E/A will be changed and will be ≥ 2. In some cases due to the increase pressure gradient between atrium and ventricle the A wave will become so small that it can't be seen in echocardiography and in such cases the E/A ratio can reach ≥ 5. But also when the filling pressure becomes so high there will be abrupt filling of the ventricle and stoppage. So in these cases other parameters are assessed like IVRT interval which should be ≤ 70 millisecond, DT should be < 160 milli seconds and E/e' ratio more than 15 for diagnosing.

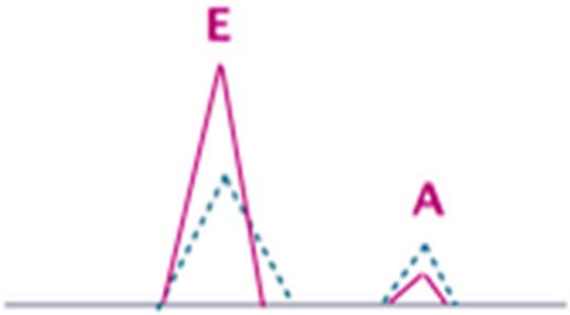


FIG : 15 Restrictive filling pattern: the E-wave is more than twice the size of the A-wave

GRADE 4 DIASTOLIC DYSFUNCTION- Irreversible restrictive filling Pattern -

This advanced form of diastolic dysfunction that is grade 4 differs from grade 3 only by the fact that the restrictive pattern is not changed by Valsalva manoeuvre and is because the valsalva may not be adequate or filling pressure is too high to be altered by valsalva manoeuvre.

As per European society of cardiology guidelines on the diagnosis of HFPEF recommends the exclusion of HFpEF in the setting of normal BNP level (<100 pg/ml) and in present study the values >100 pg/ml were taken as significant to make the diagnosis in patients of HFPEF with signs and symptoms of heart failure, LVEF > 50% and the value of E/e' in between 8 and 15[62].

Veldhuisen et al[63] Studied in 615 patients about the prognosis in cases of HFPEF and HFREF and founded that BNP levels were less in patients with HFPEF than in patients with HF with reduced LVEF, but the prognosis of the patients who were having HFPEF is same as of those patients with reduced LVEF.

Gottdieneret al [64] studied congestive heart failure outcomes in 5888 patients who were 65 years of age. Out of 5532 participants, 269 patients had congestive heart failure, out of which LVF was normal in 63%, borderline decreased in 15%, and grossly impaired in 22% and concluded that more deaths were reported from heart failure in patients with normal systolic function because LV function is normal than impaired in elderly persons with heart failure.

Iwanaga Y et al[65] in 2006 studied in 160 consecutive patients presenting with HF, and measured plasma BNP levels as well as 2D Echo and cardiac catheterization was also done. From echocardiographic and hemodynamic data Systolic and diastolic

meridional wall stress was also calculated and concluded that Left ventricular end diastolic pressure had significant correlation with BNP values, but the correlation between end diastolic wall stress and plasma BNP [$p < 0.001$] was more strong but as compared with Systolic Heart Failure and Diastolic Heart Failure, the BNP level was significantly higher in SHF ($p < 0.001$) and concluded that plasma BNP levels reflect EDWS of left ventricle, not only in patients with systolic dysfunction, but also in patients with DD.

Lee DS et al studied[66] in Framingham Heart study about the risk factors, clinical characteristics during the onset of HF and long-term survival in cases according to ejection fraction ≤45% in 314(59%) vs. >45% in 220(41%) and found that HTN, AF, female gender were more associated with HFPEF while in HFREF MI was most common cause.

Bursi et al [67] studied the risk factors in 308 patients and found out that the patients with HFPEF are older(77%), hypertensive(86%), female gender(57%), mean BMI (29.6kg/m2), DM(36%), AF(31%), renal impairment(11%), hyperlipidaemia (38%), COPD(38%) and less likely to have CAD.

Tsuchihashi-Makaya M et al[68] compared the outcomes by using registry data base in Japan from 164 hospitals in 2675 patients who had mean follow up of 2.4 yrs in HFPEF vs. HFREF in view >50% in 429 subjects were more likely to be elderly, female gender, having HTN & Atrial Fibrillation, as compared with those with HFREF in 985 patients EF < 40 % in which ischemic cause was the likely etiology. The mortality in hospital and after discharge seen in patients of HFPEF group as compared to HFREF group was similar.

Devereux RB et al [69] studied CHF in a population based sample with normal systolic function. In this study 95 patients were taken out of 3184 patients by their clinical parameters and by their Doppler echo parameters who presented in Congestive heart failure. Out of these 95 patients 50 had normal EF> 54%, 19 had mildly reduced Ejection fraction 40% -54%, and 26 had EF≤40%. But when compared with patients with no signs of congestive heart failure vs. patients with CHF with preserved EF had higher creatinine levels and higher prevalence's of DM (60%-70% vs 50%) and HTN (75%-96% vs. 46%), disproportionately women, elderly age group, and higher systolic blood pressure prolonged DT and a reduced E/A ratio, higher LV mass and relative wall thickness and higher BMI , whereas those with CHF and EF≤40% had high E/A ratios and short DT.

Knudsen CW et al [70] did a study in 292 patients presenting with acute dyspnea who were having permanent or paroxysmal atrial fibrillation to see the diagnostic utilization of BNP in patients either having heart failure or without it. In patients without heart failure it was seen that there were increased levels of BNP, but when BNP Levels were compared in patients suffering from heart failure either having atrial fibrillation or without it levels showed no significant change. Hence concluded that in patients without heart failure AF has strong association in form of increased values of BNP and hence suggesting that a higher threshold values should be used if a patient presented with AF.

Omar Issa et al [71] studied the size of left atrium and HF related Hospitalization in Patients with DD and Preserved EF in 415 patients for 2 years and founded that patients with HFPEF had higher BMI, creatinine, beta-blocker use, and Grade 2 diastolic dysfunction when compared to the hypertensive control population.

Echocardiographic analysis demonstrated higher right ventricular systolic pressures(42.0±10.4 with p value <0.001), left ventricular mass index(126.2±32.6), E/A(1.17±0.62 with p value <0.001), and E/e'(16.4±6.7 with p value <0.001) in patients with HFpEF and similar differences were observed in most left atrial (LA) parameters including larger LA maximum and minimum volume indices, as well as smaller LA-emptying fractions in the heart failure group and found that LA minimum volume index(40.2±14.8 with p value < 0.001) have the strongest association with heart failure hospitalization after adjustment for creatinine and BMI .

Delas Fuentes L et al [72] studied the extent to which the criteria for metabolic syndrome predict left ventricular (LV) structure and function in 607 patients and found that Patients who were having metabolic syndrome were having diastolic dysfunction of left ventricle which was independent of Left ventricular mass. And this could explain the increased risk of morbidity related to cardiovascular involvement and mortality associated with metabolic syndrome.

NirAyalon et al [73] did a study to see preclinical left ventricular diastolic dysfunction amongst metabolic syndrome patients who had no cardiovascular disease. In the study 90 patients were enrolled and were compared with control group. All patients went echocardiography along with tissue Doppler. The study observed that higher left atrial diameter and left ventricular mass with low E/A ratio was seen in metabolic syndrome patients.

Venkatesh Y. Anjan, et al [74] did a study in Northwestern university among 159 patients under HFPEF programme. They compared clinical characters along with echocardiography parameters in HFPEF patients having normal and increased BNP levels. They observed that normal BNP values were common in females, young age

group. However pulmonary capillary wedge pressure was same in both the groups. Higher BNP levels were associated with structural and functional abnormalities of the ventricles with decreased diastolic function. They found that 29% of symptomatic patients had normal BNP values but had increased pulmonary capillary wedge pressure in HFpEF. Hence BNP was an important prognostic marker in patients of HFpEF but normal BNP values in symptomatic patients did not rule out chances of HFpEF.

Iwanaga Y et al [75] in 2007 did a study in 295 patients and checked for BNP levels along with echocardiography and cardiac catheterization among overweight and obese patients. They observed that BMI levels were inversely related to BMI and end diastolic wall stress of the patients.

Mehra MR et al[76] examined the association between BNP in heart failure in 318 patients during 1 year and BNP levels were compared in obese and non obese and found that one-fourth were lean , one-third overweight and 35% obese. The results showed that Levels of BNP were certainly lower in obese than in non obese patients, even though a similar severity of HF and cytokine levels.

McCord J et al[77] evaluated relationships between BNP, BMI, and CHF in 1586 subjects in the Breathing Not Properly Multinational Study who had acute difficulty in breathing and subjects with more Basal metabolic index were younger on observation but were similarly as likely to have heart failure vs non cardiac sources of difficulty in breathing and 3-fold difference was seen in mean BNP values at the starting and ending of the BMI groups and results showed that BNP levels are inverse to BMI.

Krauser DG et al [78] did a study in 204 patients having acute CHF to see association of amino terminal pro BNP, BNP and BMI levels. The study showed pro BNP levels may be falsely negative among overweight patients but bnp levels were somewhat more accurate.

Khan AM et al [79] observed the relation in 7770 subjects between obesity and BNP to see role of increased insulin levels along with testosterone levels. They showed that obesity had low N-BNP levels along with increase insulin resistance among them. On other hand, insulin sensitive patients had minimal reduction in BNP levels.

Tsutamoto T et al [80] studied to find out the relationship between BNP levels, renal function and the severity of CHF in 366 subjects and the eGFR was calculated by cockroft gault equation and these patients were divided into two groups, one with GFR $\geq$ 60 ml/min and second with GFR $\leq$ 60 ml/min with all baseline and echo parameters were same and found that BNP values were increased in patients with GFR values less than 60 ml/min due to decrease clearance from kidneys.

Matsumoto M et al [81] studied the effects of anemia on levels of plasma brain natriuretic peptide in healthy subjects . Total of 1036 patients were enrolled and found that in 292 patients, the abnormal BNP levels were present and frequency was higher in women compared to men (31% vs 14%) and thus evaluated levels of BNP is inversely correlated with hemoglobin and hence concluded that in healthy subjects elevated levels of BNP plays a major role in anemia.

Hirofumi Ueno et al [82] studied the combined effect of anemia with raised B-type natriuretic peptide levels which significantly enlightens an increased risk for major adverse cardiac events and 185 patients were included in the study with predefined values for anemia and assessed the adverse cardiac events and found that in anemia, the major cardiac adverse event had high BNP levels and thus, concluded the synergistic effect of anemia in addition to high BNP levels significantly enlightens an increased risk for MACE.

Wu AH et al [83] did a study among patients with heart failure and without heart failure to see for relation between their haemoglobin and BNP levels. They found that significant low haemoglobin levels were seen in patients having heart failure of class III-IV NYHA as compared to patients having heart failure of class I-II NYHA. They also saw the relation between the severity of anaemia and BNP levels and concluded that BNP levels were higher as patients symptoms increased and severity of anaemia increased.

Lund LHet al[84] conducted a study 'Association between use of renin-angiotensin system antagonists and mortality in patients with heart failure and preserved ejection fraction'. 41,791 patients were enrolled from 64 hospitals. Out Of these, 16,216 patients with HFPEF (ejection fraction ≥40%; mean age, 75 years; 46% women) were either treated (n = 12,543) or not treated (n = 3673) with RAS antagonists and found that 1-year survival was 77% for treated patients vs 72% for untreated patients and concluded that, in patients with HFPEF the decrease use of RAS antagonists was associated with lower all-cause mortality.

In the CHARM-Preserved Trial Yusuf S et al [85] studied effects of candesartan in patients with chronic heart failure and preserved LV ejection fraction in March, 1999, and July 2000 in 3,023 patients and patients were prescribed candesartan (n=1514, target dose 32 mg OD) or matching placebo (n=1509 with a Median follow-up of 36.6 months. 333 (22%) patients in the candesartan and 366 (24%) in the placebo group experienced the primary outcome). No difference between cardiovascular death between groups (170 vs 170), but less patients in the candesartan group than in the placebo group were admitted to hospital for CHF once (230 vs 279, p=0.017) or multiple times and concluded that Candesartan do have a moderate role in preventing admissions for CHF among patients who have heart failure and LVEF higher than 40%.

In the Aldo-DHF randomized controlled trial [86] studied Effectiveness of diuretic spironolactone on DF and the exercise capacity in patients with HFPEF between March 2007 and April 2012 and included 422 patients with average age of 67 years. Out of which 213 patients with 52 % being females were given spironolactone 25 mg on daily basis and in 219 patients were given matching placebo. Patients were followed up for a period of 12 months and concluded that Diastolic function in the form of E/e' decreased from 12.7 to 12.1 with spironolactone and increased from 12.8 to 13 with placebo group which was significantly proved by P value <0.001. Peak VO2 did not significantly change with spironolactone vs placebo from 16.3 to 16.8 mL/min/kg and from 16.4 to 16.9 ml/min/kg, Spironolactone causes left ventricular remodeling with difference: 6 g/m^2 to 1 g/m^2; and improved biomarker BNP and mildly improved 6-minute walking distance. But Spironolactone causes slight hyperkalemia and decreased eGFR but didn't affected the hospitalization rate.

PEP –CHF Study [87] was a randomized double blind trial, comparing placebo with perindopril 4mg/day in 850 patients aged > 70year with a diagnosis of heart failure treated with a diuretics and an echocardiogram suggesting diastolic dysfunction for a mean period of 2.1 years. The primary end point was a composite of all-cause mortality and related number of hospitalizations improved symptoms and exercise capacity and fewer hospitalizations for heart failure in the first year were observed in perindopril group.

I-PRESERVE Study [88] showed a neutral outcome when angiotensin II receptor blocker irbesartan was compared with placebo. 3600 patients, 60 years of age or older with a clinical diagnosis of HF and EF > 45% were observed over 48 months the primary end points were death and hospitalization for cardiovascular disease.

Beta blockers effect in heart failure was studied in the SENIORS Trial [89] which had 2128 patients aged >70 years. It had a diastolic subset and compared nebivolol with placebo. The effect of beta –blockade with preserved and impaired EF.

The effect of renin – angiotensin blockade by irbesartan or ramipril in combination with diuretic on quality of life (Qol), regional and global systolic and diastolic function was assessed in HFNEF patient in the The Hong Kong Diastolic Heart Failure Study [90] in which 150 patients with HFNEF (LVEF >45%) were randomized to (1) diuretics alone, (2) diuretics plus irbesartan or (3) diuretics plus ramipril. In this typically elderly group of HF patient with normal LVEF, Diuretic therapy significant improved symptoms and neither irbesartan nor ramipril marginally improved LV function, and lowered NT –proBNP over 1 year.

The SWEDIC Study, a double blind multi-Centre study investigates the effects of carvedilol as an addition to conventional treatment (e.g. diuretics and/or ACE – inhibitors and /or digoxin) on diastolic function in 113 symptomatic patients with HF with preserved systolic function and evidence of diastolic dysfunction determined by Doppler echocardiography.[91] The patients received either carvedilol or matching placebo in addition to conventional treatment. At the end of the study there was a statistically significant improvement in E: A ratio in patients treated with carvedilol (0.72 to 0.83) vs placebo (0.71to 0.76) ($p<0.05$).

Wak forest and MCC -135 study is another such on going relevant trail[92] digoxin has been shown to be of benefit in diastolic heart failure, although the result of the digitalis investigation group trail suggested that patients with diastolic heart failure had fewer symptoms and hospitalization when treated with digoxin [93] however in another trial the use of digoxin is also not associated with any benefit in these patients.[94]

Recent studies found that Non-Cardiac Comorbidities like Diabetes, Obesity is common in the general population and the prevalence of obesity has been rising at an alarming rate over the past several years. Obesity has been associated with adverse cardiac remodeling and dysfunction in both experimental models and in humans, and obesity is associated with a high output state. Together, these pathophysiologic abnormalities result in the HF syndrome, often with a preserved EF. Thus, the high prevalence of obesity in the general population (and the increases in rates of obesity over time) contributes to the epidemic of HFpEF. Accordingly, obesity is highly prevalent in HFpEF (32–46 %), and high body mass index (BMI) is known to be a risk factor for HFpEF. [95-98] In a recent Framingham Heart Study report, higher BMI

was shown to be a predictor of HFpEF but not HFrEF.[99] In few studies treatment with insulin improved post meal glucose values and was associated with improved diastolic dysfunction and improved myocardial perfusion. [100] As an another choice to medical management if focused on dietary and lifestyle modifications which can be the key parts in the prevention and management of heart failure and could be extremely beneficial. A low-sodium rich diet known as the DASH diet in a larger group of studies has been shown that it significantly reduces the incidence of HF[101]. In the Swedish Mammography Cohort the women who were compliant with the DASH diet had a 37 % less chance of development of HF after a mean follow up of 7 years. The DASH diet is also beneficial in decreasing the incidences of HTN, Stroke, and Hyperlipidemia which are commonly seen as comorbid conditions in HFPEF.[102-103] Non-pharmacologic treatment options such as yoga and devices that mimic this approach[104] hold promise in the treatment of hypertension that often leads to HFPEF without the side effects and expense of money.

CLASS	INDICATION	LEVEL OF EVIDENCE
I (indicated)	Systolic and diastolic blood pressure should be controlled in accordance with published clinical practice guidelines to prevent morbidity.	B
	Diuretics should be used for relief of symptoms due to volume overload.	C
IIa (good supportive evidence)	Coronary revascularization is reasonable in patients with coronary artery disease in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic heart failure.	C
	Management of atrial fibrillation according to published clinical practice guidelines is reasonable to improve symptomatic heart failure.	C
	The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure.	C
IIb (weak supportive evidence)	The use of ARBs might be considered to decrease hospitalizations.	B
III (no benefit)	Routine use of nutritional supplements is not recommended.	C

FIG : 16 – ACC/AHA/HFSA/ESC Guidelines for the treatment of patients with stage C Heart Failure And Preserved Left Ventricular Ejection Fraction(HFPEF)

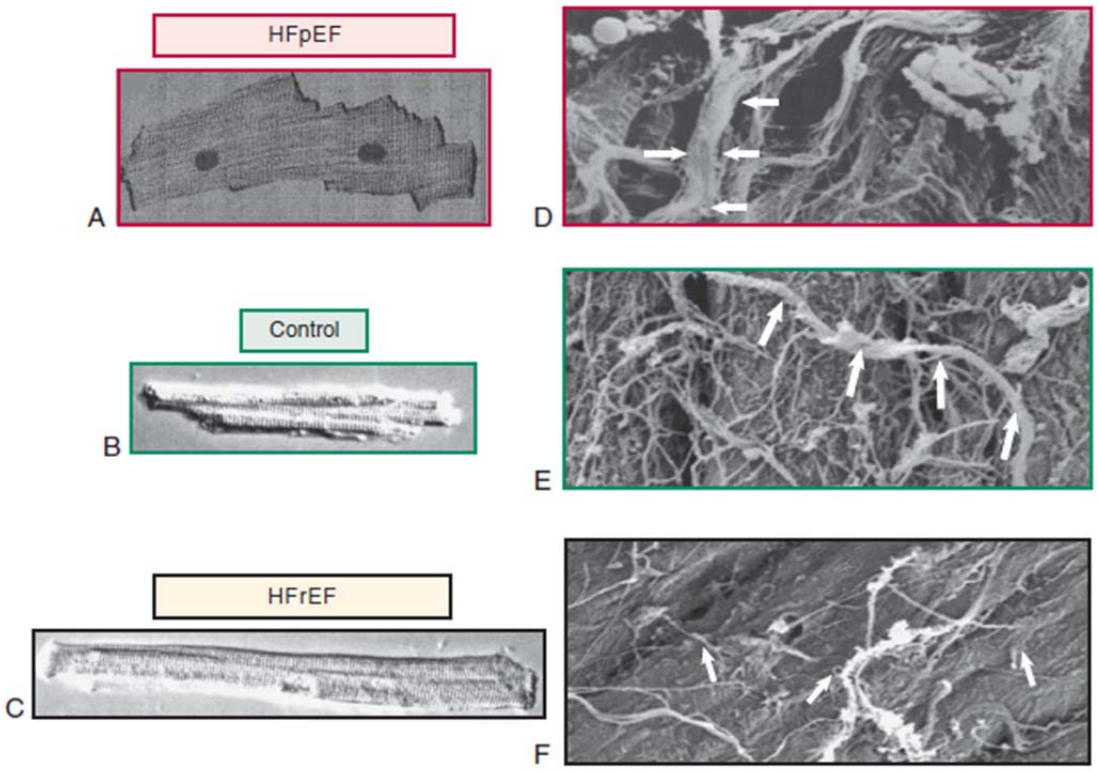


FIG : 17 Cardiomyocyte structure changes (A-C) and changes of extracellular matrix fibrillar collagen (D-F) in HFpEF (outlined in *red*) versus HFrEF (outlined in *black*) versus findings in referent control group (outlined in *green*).

- In HFpEF there is concentric cardiomyocyte remodeling with increased diameter. But there is no change in length and there is an increased fibrillar collagen thickness, number and content.
- In HFrEF there is eccentric cardiomyocyte remodeling with the length increased. But there is no change in width and fibrillar collagen degradation and abnormal structure and turnover. *Arrows* indicate fibrillar collagen.[105]

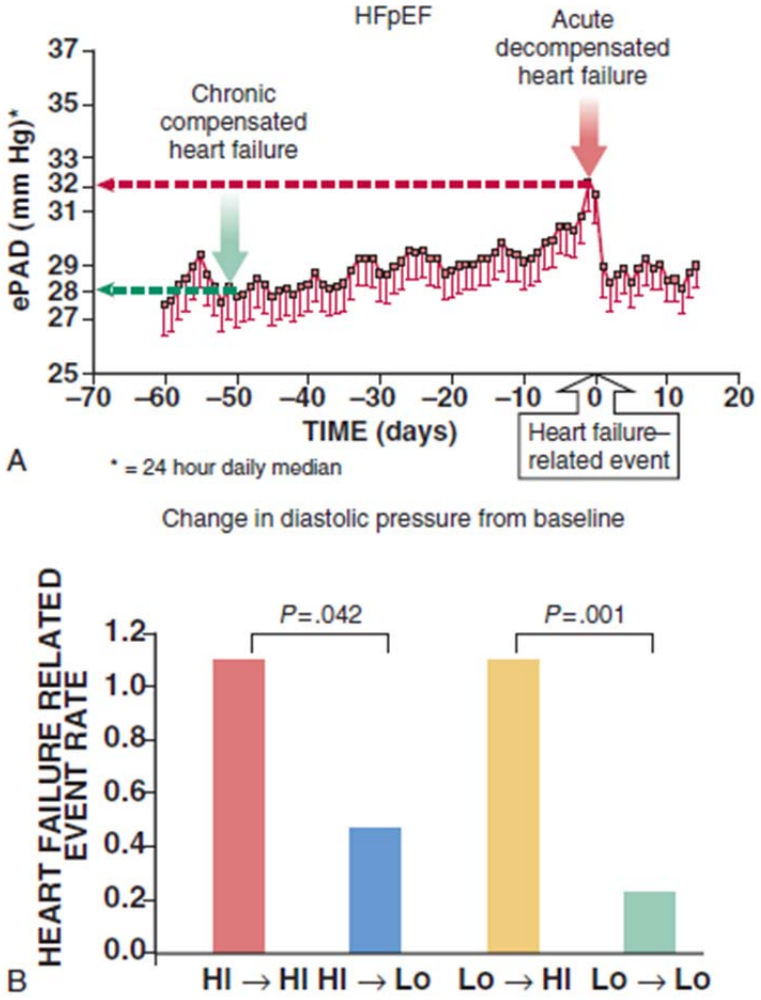


FIG : 18 - A, Patients with HFpEF who are considered to be in good compensation by physician may have increased LV diastolic pressure (indexed here as ePAD)with the development of ADHF necessitating hospital admission, B, Both baseline LV diastolic filling pressure and changes in filling pressure are good predictors of future ADHF events.[106]

MATERIALS AND METHODS

1. Material and methods

A. Study Design : Cross sectional study

B. Study Period : 18 months

Sampling Population:

All the patients attending Cardiology and Medicine OPD And IPD, Sree Mookambika Institute of Medical Sciences, Kulasekharam during the decided study period.

a. Inclusion Criteria:

- Age > 18 and willing to give consent
- Presence of symptoms and signs of Congestive Heart failure at the time of presentation
- LVEF >50% on detailed Transthoracic echocardiography examination.
- Presence of LV Diastolic Dysfunction

b. Exclusion Criteria

- Patients with LVEF <50% on Transthoracic Echocardiography Examination.
- Patients with LV dilation. (LVIDd >55mm).
- Patients with valvular heart disease.
- Patient not giving consent.

METHOD OF COLLECTION OF DATA

All the patients of suspected clinical diagnosis of heart failure on basis of Framingham's criteria were taken up for the study.

The Framingham's criteria are as follows:

Diagnosis of heart failure requires 2 or major criteria OR 1 major or 2 minor criteria:

Major criteria:

1. Acute pulmonary edema
2. Cardiomegaly
3. Hepatojuglar reflux
4. Neck veins distension
5. PND or orthopnea
6. Pulmonary rales
7. Third heart sound(S3 gallop rhythm)
8. Weight loss > 4.5 kg in 5 days in response to treatment.

Minor criteria

1. Ankle edema
2. Dyspnea on exertion
3. Hepatomegaly
4. Nocturnal cough
5. Pleural effusion
6. Tachychardia

a. Sample Size Calculation:

[$n = 4pq/d^2$; p = 67% (Jorge AJL et al study)]

p = HFPEF with mean BNP value of 153.3± 123.1pg/ml = 67%

q = 100 – p = 100 – 67 =33

d = 20% of p = 20% of 67 = 13.4

$n = 4x67x33/ (13.4)^2 = 8844/179.56$

= 49.25 = 50

D. Study Procedure

All eligible patients enrolled, written and informed consent obtained from them. Apart from demographic details, detailed history taken and did physical examination and total 5 ml of blood was collected and investigated and suspected heart failure patients went through Transthoracic echocardiography and BNP testing done to diagnose the heart failure with preserved ejection fraction and classified according to diagnostic dysfunction.

For BNP sampling :

- Specimen type - Blood plasma
- Container - Vacutainer, lavender top (EDTA)
- Collection method - Venipuncture
- Specimen volume - 2 mL
- Other instructions - Spin down and freeze plasma immediately; patient age and sex required

E. Data Collection Methods including Setting and Periodicity:

All the pertinent data was collected in predesigned data collection form and was entered into Microsoft Excel 2013 and analysis was done in SPSS Software version 20.0.

INVESTIGATION TO BE CONDUCTED ON PATIENTS FOR THE STUDY

All such patients were subsequently submitted to detailed 2D/Doppler echocardiography study using EPIQ 7 Philips adult 4D Echo machine using sector probe of frequency range between 3-5 Hz.

Ejection fraction was calculated by Modified Simpsons method.

Left atrium volume index was calculated by using Simpson's method for volume determination divided by body surface area.

Mitral inflow velocity examination with pulsed wave Doppler was done in apical 4 chamber view by placing sample volume at tip of mitral valve leaflets.

Doppler Parameters

Detailed mitral inflow velocity study measuring transmitral E wave and A wave velocity, E/A ratio were studied.

The Diastolic dysfunction was graded as:

Grade I- Impaired relaxation with normal filling pressure.

Grade II -moderate dysfunction, pseudonormalised mitral inflow pattern.

Grade III-severe reversible, reversible restrictive (High Filling Pressure)

Grade IV-severe irreversible dysfunction irreversible restrictive pattern (High Filling Pressure)

Simultaneous BNP levels was done by an automated quantitative test by using plasma using the ELFA (Enzyme-Linked Fluorescent Assay) technique.

As per European society of cardiology guidelines on the diagnosis of HFPEF, BNP value is divided into 3 groups as

<100 pg/ml which is normal value

100 – 400 pg/ml denotes mild to moderate heart failure

>400 pg/ ml suggests Severe heart failure which were compared with various parameters associated with HFPEF.

Other investigations that were done are :

Complete blood count **(**Hb, TLC, DLC)

Renal function test (RFT)

Liver function test (LFT)

Lipid Profile

RESULTS

TABLE 1

Number and percentage of patients based on Gender

GENDER	NUMBER OF PATIENTS	PERCENTAGE
MALE	19	38
FEMALE	31	62

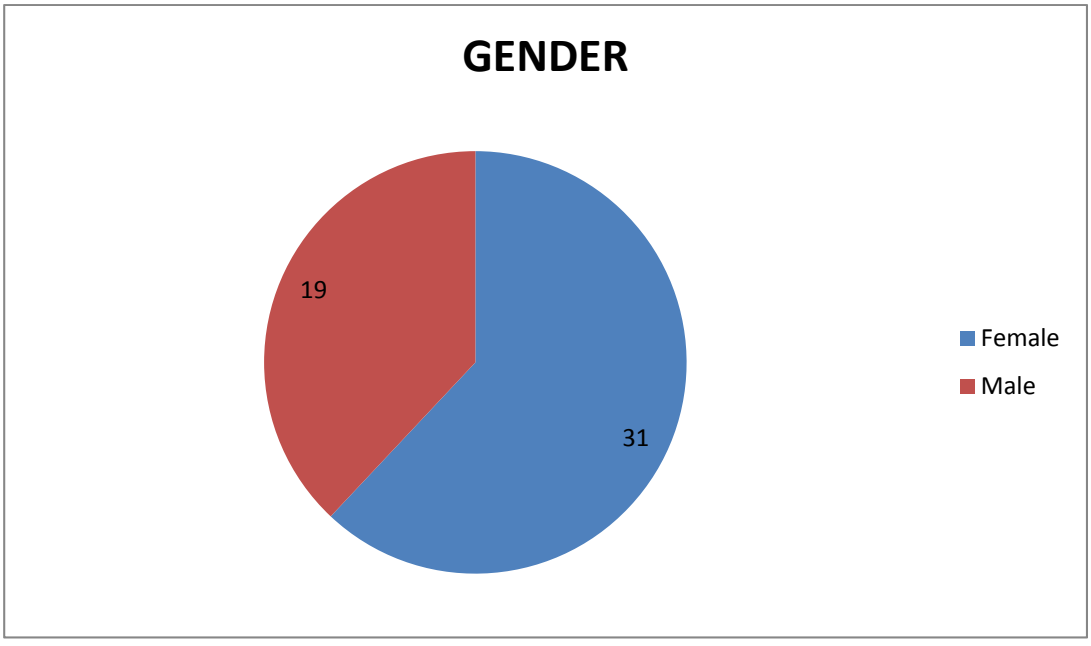


FIG : 19 Number of patients based on Gender

In my study total no of patients 50 out of which 31 females (62 %) and 19 male (38%).

TABLE 2

Number and percentage of patients based on BNP Value

BNP LEVEL (pg/ml)	NUMBER OF PATIENTS	PERCENTAGE (%)
<100	6	12
100-400	9	18
>400	35	70

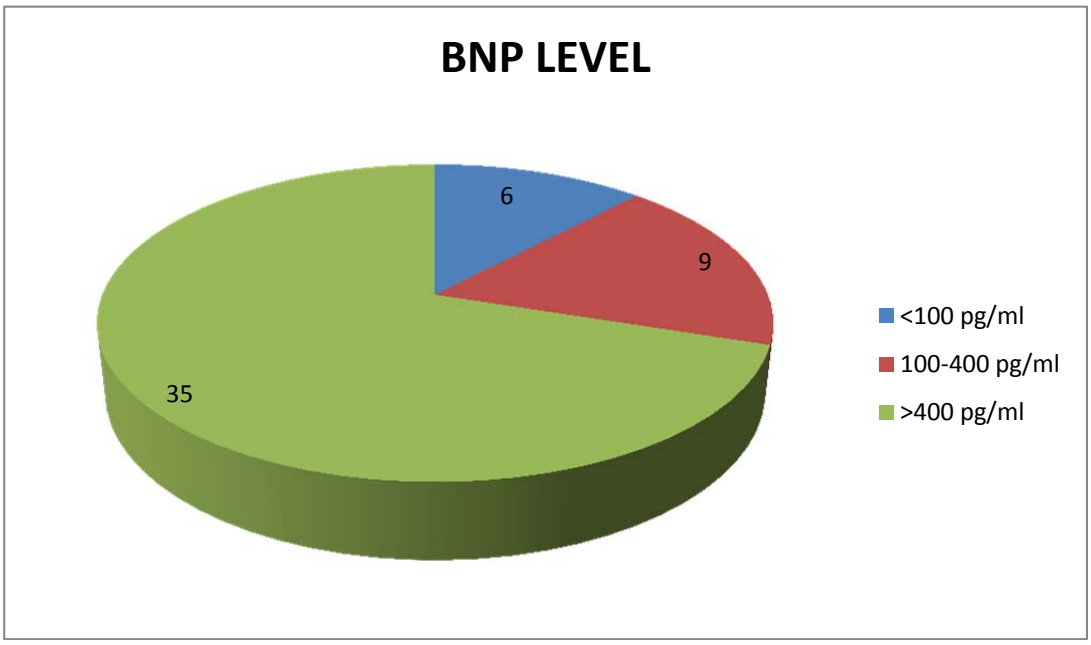


FIG : 20 –Number of patients based on BNP Value

Out of 50 patients 35 cases (70 %) of having BNP > 400 pg/ ml followed by 9 cases (18%) in 100-400 pg/ml range and then 6 people (12%) having < 100 pg/ml.

TABLE 3

Number and percentage of patients based on Diastolic Dysfunction Type

DIASTOLIC DYSFUNCTION TYPE	NUMBER OF PATIENTS	PERCENTAGE
TYPE 1	**23**	**46**
TYPE 2	**12**	**24**
TYPE 3	**15**	**30**

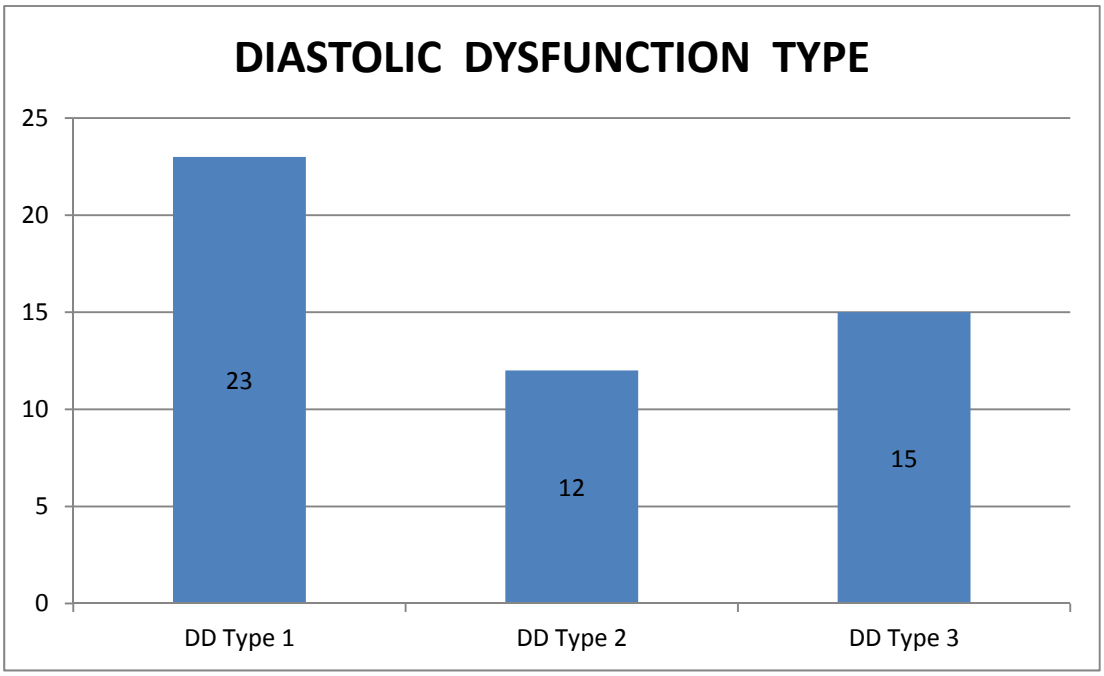


FIG : 21 –Number of patients based on DD Type

Out of 50 patients 23 cases(46 %) having DD Type 1 followed by 15 cases (30 %) with DD Type 3 and then 12 cases (24 %) with DD Type 2.

TABLE 4

AGE DISTRIBUTION OF PATIENTS WITH BNP VALUE IN HFPEF

Age / BNP	<100 pg/ml	100-400 pg/ml	>400 pg/ml	Grand total
40-50YEARS	2 (25%)	2 (25%)	4 (50%)	8
51-60 YEARS	3 (22%)	2 (14%)	9 (64%)	14
61-70 YEARS	1 (6%)	3 (18%)	13 (76%)	17
>70 YEARS		2 (18%)	9 (82%)	11
Grand total	**6 (12%)**	**9 (18%)**	**35 (70%)**	**50**

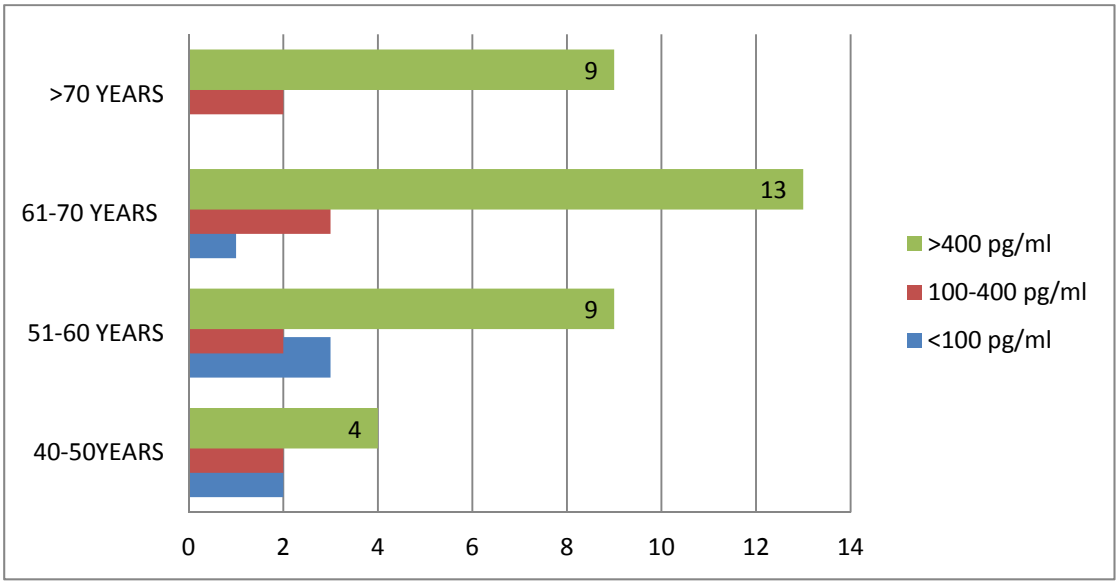


FIG : 22 AGE DISTRIBUTION WITH BNP VALUE

As seen from this table, maximum number of cases was in age group of 61-70(34%) followed by 51- 60 years (28%), >70 years (22%) and 40-50 years(16%).

In the age group of 40-50 years 2 cases (25%) were having BNP below 100 pg/ml , 2 (25%) and 4(50%) cases were having 100-400 pg/ml and >400 pg/ml BNP respectively.

In the age group of 51-60 years 3 (22%), 2(14%) and 9(64%) cases were having BNP <100 pg/ml, 100-400 pg/ml and >400 pg/ml BNP respectively.

In the age group of 61-70 years 1(6%) case was having BNP below 100 pg/ml, 3(18%) and 13(76%) cases were having 100-400 pg/ml and >400 pg/ml BNP respectively.

In the age group of >70 years No case was having BNP below 100 pg/ml but 2(18%) and 9(82%) cases were having 100-400 pg/ml and >400 pg/ml BNP respectively.

TABLE 5

DISTRIBUTION ACCORDING TO SEX WITH BNP VALUE IN HFPEF

Sex/BNP	<100 pg/ml	100-400 pg/ml	>400 pg/ml	Grand Total
Female	5 (16%)	5 (16%)	21 (68%)	31
Male	1 (5%)	4 (21%)	14 (74%)	19
Grand Total	**6 (12%)**	**9 (18%)**	**35 (70%)**	**50**

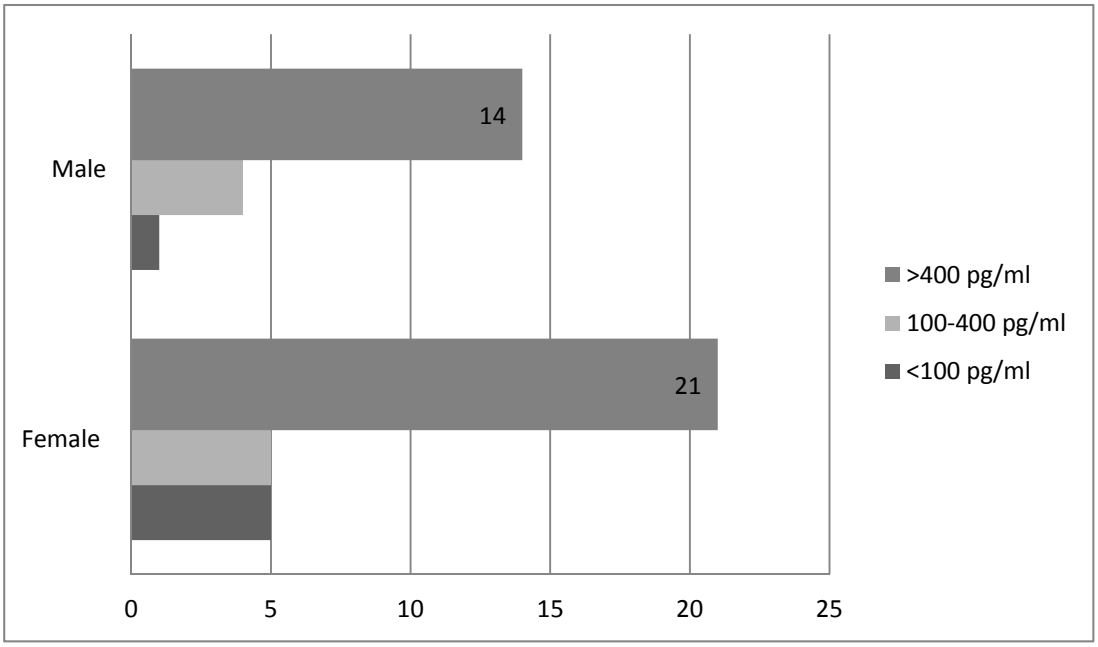


FIG : 23 – Correlation between Gender and BNP value

As seen from this table, majority of the cases were female, with female: male ratio being 1.6: 1 with 62 % of the patients being females and 38 % males.

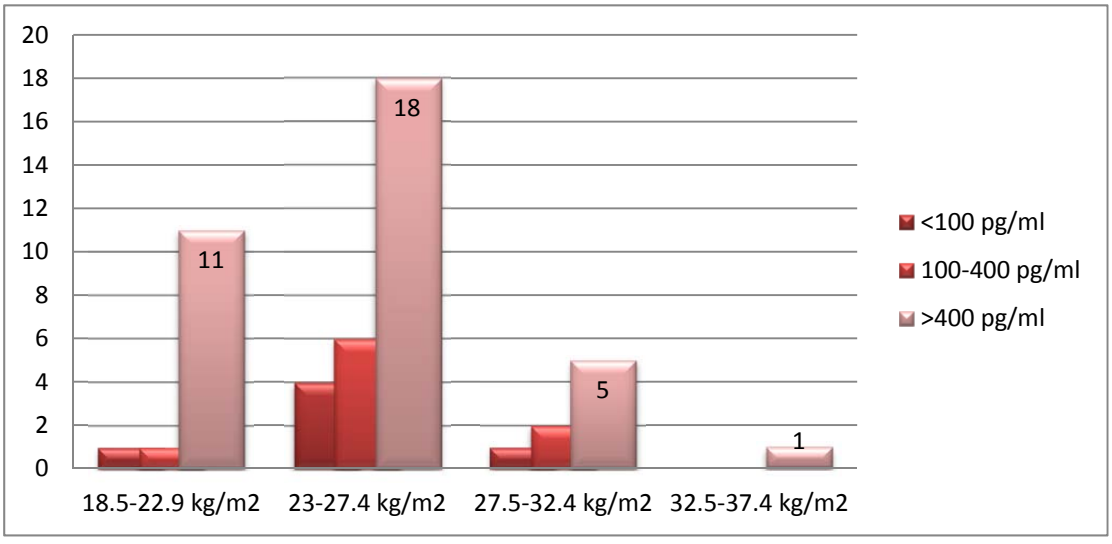
In females 5 cases (16%), 5 (16%), 21 (68%) were having BNP value <100 pg/ml, 100-400 pg/ml, >400 pg/ml respectively.

In males 1 case (5%), 4 (21%), 14 (74%) were having BNP value <100 pg/ml, 100-400 pg/ml, >400 pg/ml respectively.

TABLE -6

BODY MASS INDEX (BMI) IN PATIENTS WITH BNP VALUE IN HFPEF

BMI/BNP	<100 pg/ml	100-400 pg/ml	>400 pg/ml	Grand Total
18.5-22.9 kg/m2	1 (8%)	1 (8%)	11(84%)	13
23-27.4 kg/m2	4 (14%)	6 (21%)	18 (65%)	28
27.5-32.4 kg/m2	1 (13%)	2 (25%)	5(62%)	8
32.5-37.4 kg/m2			1 (100%)	1
Grand Total	**6**	**9**	**35**	**50**



BMI = BODY MASS INDEX GRADED ACCORDING TO ASIAN CRITERIA

FIG : 24 – BMI vs BNP Graph

As seen from the table above majority of the cases were overweight (56%) with BMI of 23-27.4 kg/m^2, followed by 26 % of the patients were in the normal range with BMI of 18.5-22.9 kg/m^2. 16% of the patients were obese i.e. BMI 27.5-32.4 kg/m^2 and only 2 % of the patients were in the range of 32.5-37.4 kg/m^2 that is very obese.

In Normal BMI group i.e. 18.5-22.9 kg/m^2 1 case (8%), 1 (8%), 11 (84%) were having BNP value <100 pg/ml, 100-400 pg/ml, >400 pg/ml respectively.

In overweight BMI group i.e. 23-27.4 kg/m^2 4 cases (14%), 6 (21%), 18 (65%) were having BNP value <100 pg/ml, 100-400 pg/ml, >400 pg/ml respectively.

In obese BMI group i.e. 27.5-32.4 kg/m^2 1 case (13%), 2 (25%), 5 (62%) were having BNP value <100 pg/ml, 100-400 pg/ml, >400 pg/ml respectively.

In very obese BMI group i.e. 32.5-37.5 kg/m^2 only 1 case was having BNP of >400 pg/ml.

The value is statistically significant (p value – 0.005)

TABLE – 7

ACC TO COMORBITIES IN 50 CASES OF HFPEF

	NUMBER OF CASES (n=50)	PERCENTAGE (%)
ANAEMIA	13/50	26
HYPERTENSION	34/50	68
CKD	2/50	4
DIABETES MELLITUS	31/50	62
HYPOTHYROIDISM	3/50	6
ATRIAL FIBRILLATION	3/50	6
CVA	3/50	6
HYPERLIPIDAEMIA	13/50	26
OSA	1/50	2

CVA(CEREBROVASCULAR ACCIDENT), CKD (CHRONIC KIDNEY DISEASE), OSA (OBSTRUCTIVE SLEEP APNOEA)

As seen from this table, it is clear that majority of the patients were hypertensive (68%) and diabetic (62%) with 26 % hyperlipidaemic and and 26 % anaemic. 6 % of the patients were having AF. Hypothyroidism was seen in 6 % of the cases, CVA in 6 %, chronic kidney disease (CKD) in 4 % and obstructive sleep apnoea (OSA) in 2 %. Thus as seen from this table majority of the patients of heart failure with preserved ejection fraction had associated co-morbid condition.

TABLE -8

RELEVANCE OF BNP IN HYPERTENSIVE AND NON HYPERTENSIVE PATIENTS IN HFPEF

BNP	<100 pg/ml	100-400 pg/ml	>400 pg/ml	Grand Total
Non Hypertensive	4 (25%)	5 (31%)	7 (44%)	16
Hypertensive	2 (6%)	4 (12%)	28 (82%)	34
Grand Total	**6 (12%)**	**9 (18%)**	**35 (70%)**	**50**

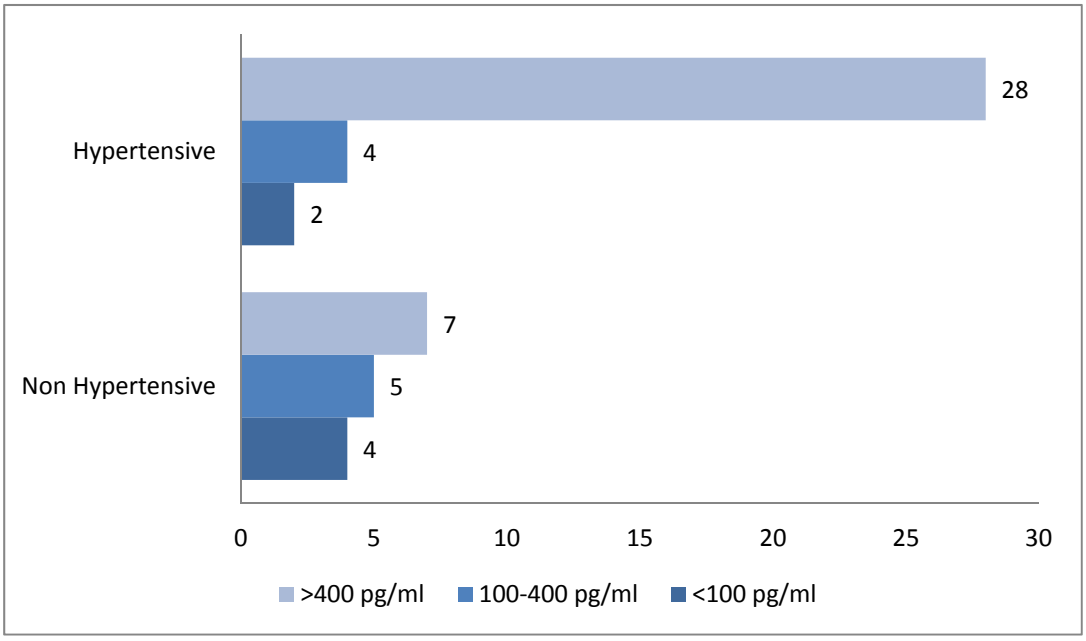


FIG : 25 - Impact of Hypertension on BNP value

As seen from this table, it is clear that majority of the patients were hypertensive (68%) and non hypertensive (32 %).

In hypertensive patients 2 cases (6%), 4 (12%), 28 (82%) were having BNP value <100 pg/ml, 100-400 pg/ml, >400 pg/ml respectively.

In Non Hypertensive patients 4 cases (25%), 5 (31%), 7 (44%)were having BNP value <100 pg/ml, >400 pg/ml respectively.

The value is statistically significant (p value – 0.019)

Table- 9

RELEVANCE OF BNP IN DIABETIC AND NON DIABETIC PATIENTS IN HFPEF

BNP	<100 pg/ml	100-400 pg/ml	>400 pg/ml	Grand Total
Non Diabetic	4 (21%)	8 (42%)	7 (37%)	19
Diabetic	2 (6%)	1 (3%)	28 (91%)	31
Grand Total	**6 (12%)**	**9 (18%)**	**35 (70%)**	**50**

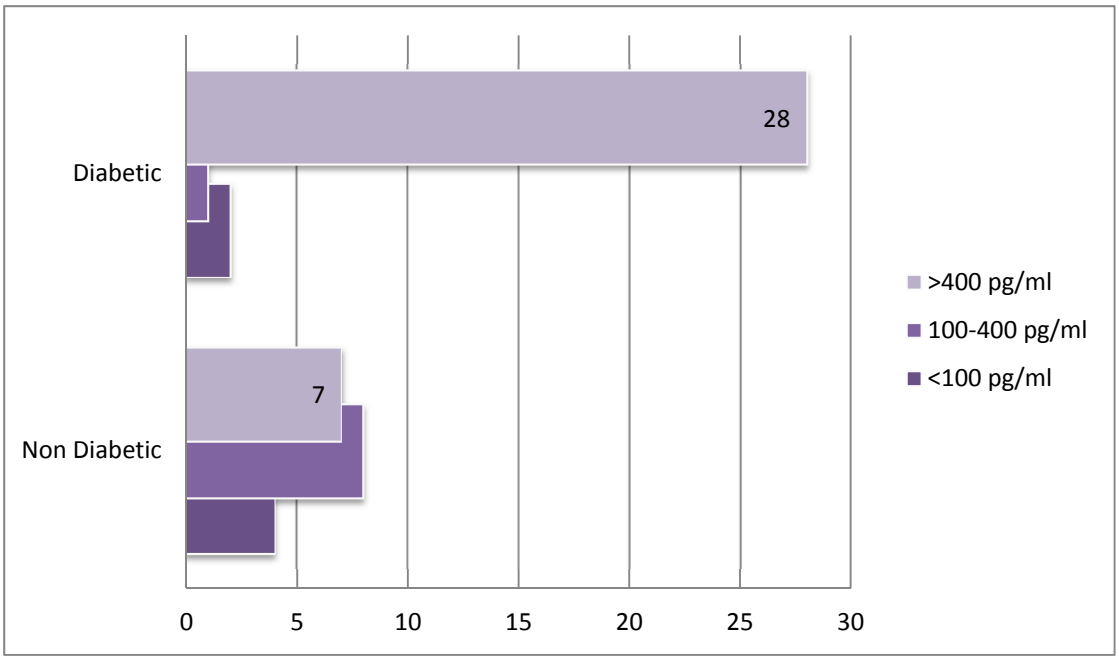


FIG : 26 – Impact of Diabetes on BNP value

As seen from this table, majority of the patients were Diabetic (62%) and Non Diabetic (38 %).

In Diabetic patients 2 cases (6%), 1 (3%), 28 (91%) were having BNP value <100 pg/ml, 100-400 pg/ml ,>400 pg/ml respectively.

In Non Diabetic patients 4 cases (21%), 8 (42%), 7 (37%) were having BNP value <100 pg/ml, 100-400 pg/ml, >400 pg/ml respectively

The value is statistically significant (p value – 0.0001)

TABLE - 10

RELEVANCE OF BNP IN DYSLIPIDEMIC AND NON DYSLIPIDEMIC PATIENTS IN HFPEF

BNP	<100 pg/ml	100-400 pg/ml	>400 pg/ml	Grand Total
Normal	6 (16%)	9 (24%)	22 (60%)	37
Dyslipidemic			13 (100%)	13
Grand Total	**6 (12%)**	**9 (18%)**	**35 (70%)**	**50**

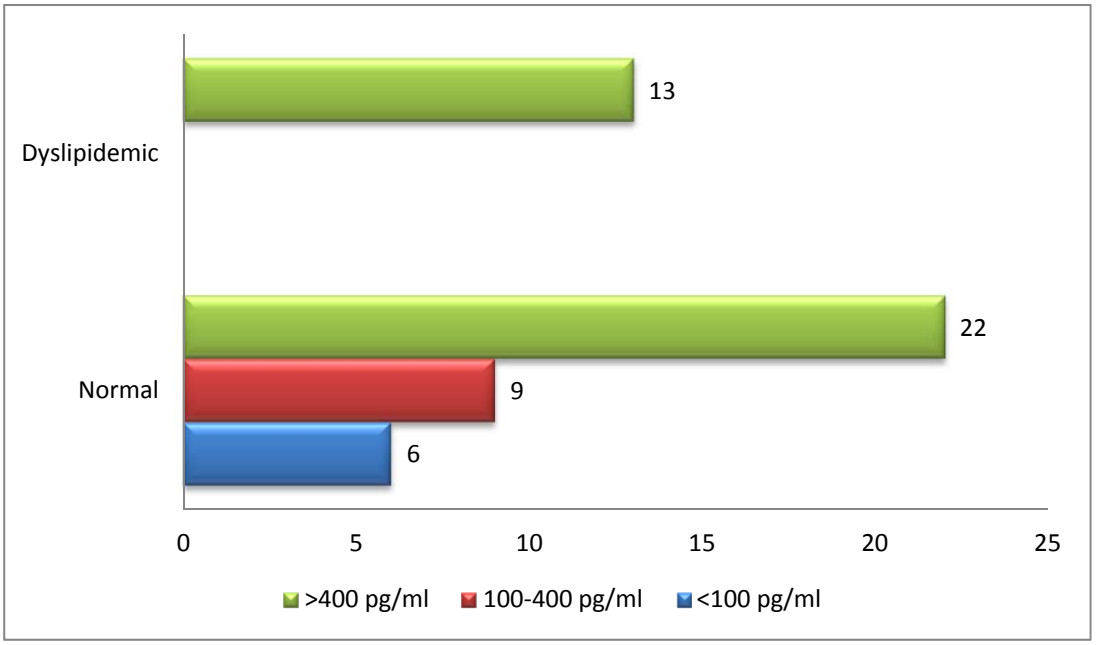


FIG : 27 – Correleation between dyslipidemia and BNP value

As seen from this table, majority of the patients were Non dyslipidemic (74%) and Dyslipdemic (26%).

In Non Dyslipdemic patients 6 cases (16%), 9 (24%) , 22 (60%) were having BNP value <100 pg/ml,100-400 pg/ml, >400 pg/ml respectively.

In Dyslipdemic patients 13 cases were having BNP value >400 pg/ml .

TABLE 11

RELEVANCE OF BNP WITH HAEMOGLOBIN LEVEL IN PATIENTS WITH HFPEF IN FEMALES

Hb (gm/dl)	BNP >100 pg/ml	100-400 pg/ml	>400 pg/ml	Grand Total
Normal (>12)	4 (17%)	3 (13%)	16 (70%)	23
Mild (10-11.9)	1 (17%)	2 (33%)	3 (50%)	6
Moderate (7- 9.9)			2 (100%)	2
Grand Total	**5 (16%)**	**5 (16%)**	**21 (68%)**	**31**

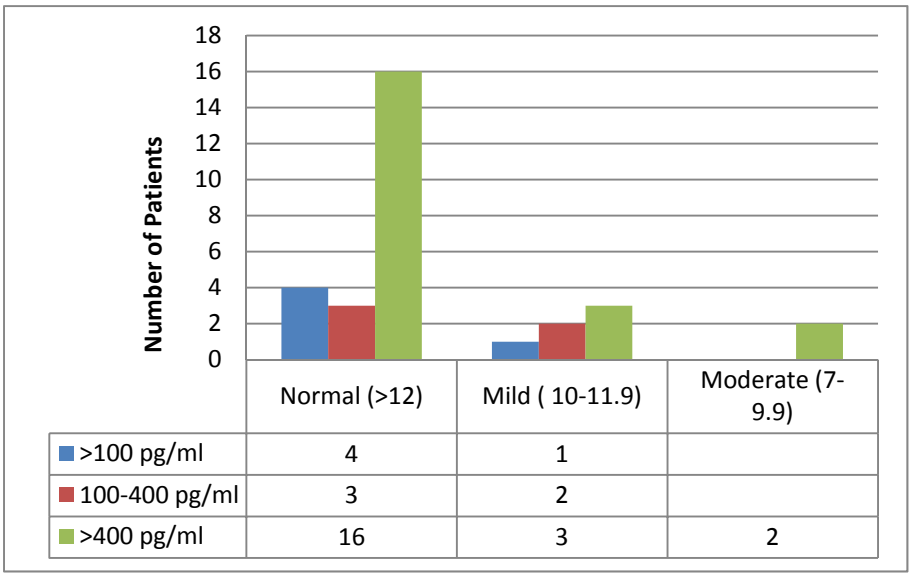


FIG : 28 – BNP value with Hb level in females

Majority of the patients in study were having normal haemoglobin level that is 23 cases (74%) followed by Mild anaemic 6 cases (19%) and then 2 Moderate anaemic cases (6 %).

In normal people 4 cases (17%) , 3 (13%) , 16 (70 %) were having BNP value <100 pg/ml,100-400 pg/ml, >400 pg/ml respectively.

In mild anaemic 1 case (17%) , 2 cases (33 %) , 3 (50 %) were having BNP value <100 pg/ml,100-400 pg/ml, >400 pg/ml respectively.

In moderate anaemic 2 cases were there which were having BNP > 400 pg/ml.

TABLE - 12

RELEVANCE OF BNP WITH HAEMOGLOBIN LEVEL IN PATIENTS WITH HFPEF IN MALES

Haemoglobin/ BNP	<100 pg/ml	100-400 pg/ml	>400 pg/ml	Grand Total
Normal (> 13)	1 (7%)	4 (29%)	9 (64%)	14
Mild (11- 12.9)			5 (100%)	5
Grand Total	**1 (5%)**	**4 (21%)**	**14 (74%)**	**19**

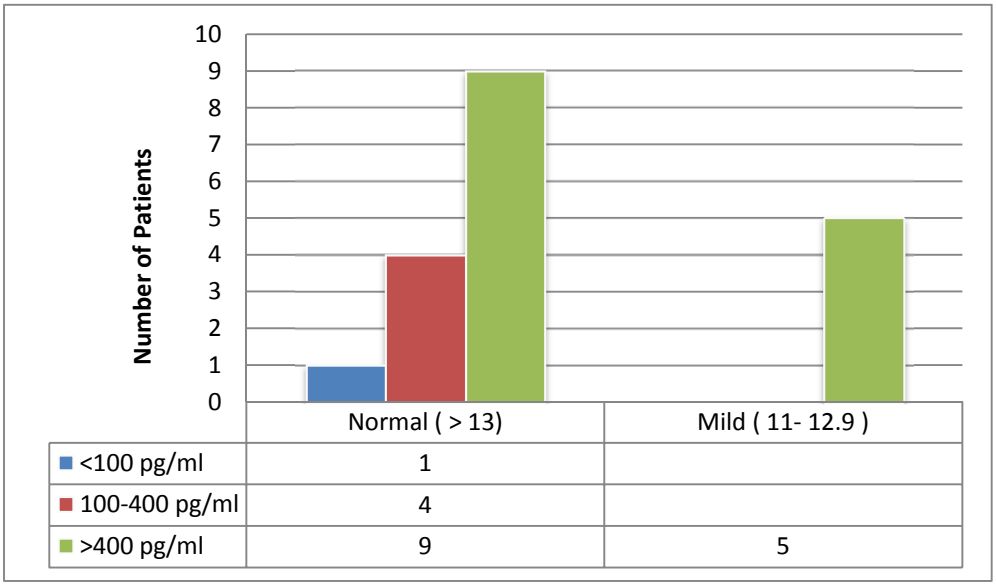


FIG : 29 - BNP value with Hb level in females

Majority of the patients in study were having normal haemoglobin level that is 14 cases (74%) followed by Mild anaemic 5 cases (26%).

In normal people 1 cases (7%) , 4 (29%) , 9(64 %) were having BNP value <100 pg/ml,100-400 pg/ml, >400 pg/ml respectively.

In mild anaemic 5 cases were there which were having BNP > 400 pg/ml.

TABLE- 13

RELEVANCE OF BNP WITH NYHA GRADING IN PATIENTS WITH HFPEF

BNP	<100 pg/ml	100-400 pg/ml	>400 pg/ml	Grand Total
NYHA GRADE 3	6 (21%)	6 (21%)	17 (58%)	29
NYHA GRADE 4		3 (14%)	18 (86%)	21
Grand Total	**6 (12%)**	**9 (18%)**	**35 (70%)**	**50**

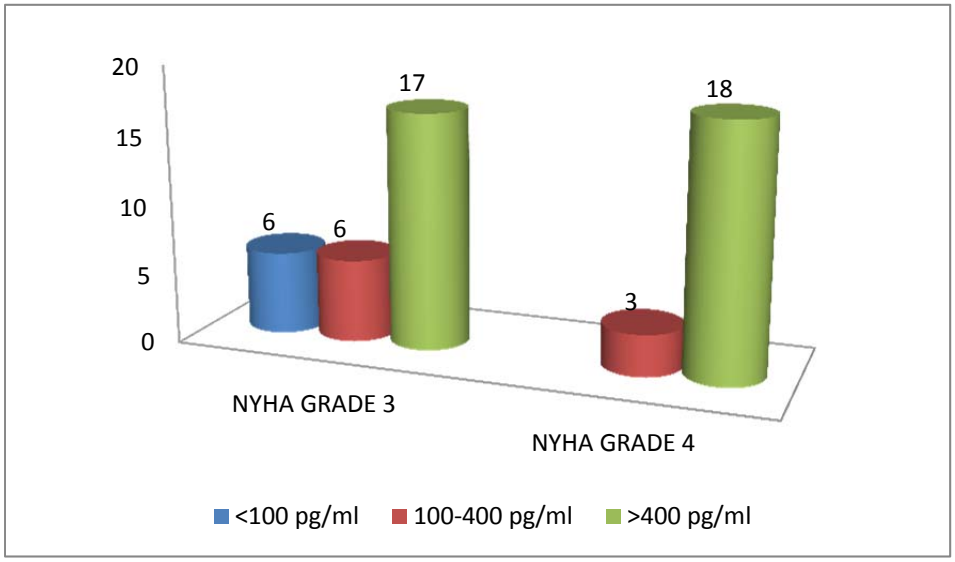


FIG : 30 – Correlation between NYHA grade and BNP value

As seen this table majority of the patients of heart failure with preserved ejection had NYHA Class III (58 %) followed by class IV (42 %), which suggests that the patients were in failure at the time of presentation.

Most of the patients were in NYHA grade III i.e patients came with dyspnea on exertion associated with orthopnea/PND which were 6 cases (21%), 6 (21%) , 17 (58%) having BNP value <100 pg/ml, 100-400 pg/ml, >400 pg/ml respectively.

3 cases (14%) , 18 (86%) were having BNP value <100 pg/ml, >400 pg/ml respectively in NYHA Grade IV patients.

The value is statistically significant (p value – 0.049)

TABLE-14

2-D ECHO PARAMETERS (M-MODE VARIABLES) 0F 50 CASES

M- MODE VARIABLES	BASELINE MEAN ± SD
LA	39.86 ± 5.97 mm (21-37mm)
LVID d	42.72 ± 7.30 mm (25-52mm)
LVID s	27.54 ± 5.2 mm (23-39 mm)
EF	58.78 ± 2.78 % (55-85%)

LA- LEFT ATRIUM, LVID D- LEFT VENTRICULAR INTERNAL DIAMETER IN DIASTOLE, LVID S- LEFT VENTRICULAR INTERNAL DIAMETER END SYSTOLE, EF- EJECTION FRACTION

As seen from the above table mean left atrium size was 39.86 ± 5.97 mm, mean left ventricular internal diameter in diastole was 42.72 ± 7.30 mm, mean left ventricular internal diameter in systole was 27.54 ± 5.2 mm with a mean normal ejection fraction of 58.78 ± 1.57 %. From this analysis it suggested that mean LA size was prominent in majority of the patients, LVIDd, LVIDs and ejection fraction was normal in all the cases.

TABLE -15

RELEVANCE OF BNP WITH LEFT ATRIAL DIAMETER IN PATIENTS WITH HFPEF

LA Diameter	<100 pg/ml	100-400 pg/ml	>400 pg/ml	Grand Total
30-40 mm	6 (26%)	7 (30%)	10 (44%)	23
>40 mm		2 (7%)	25 (93%)	27
Grand Total	**6 (12%)**	**9 (18%)**	**35 (70%)**	**50**

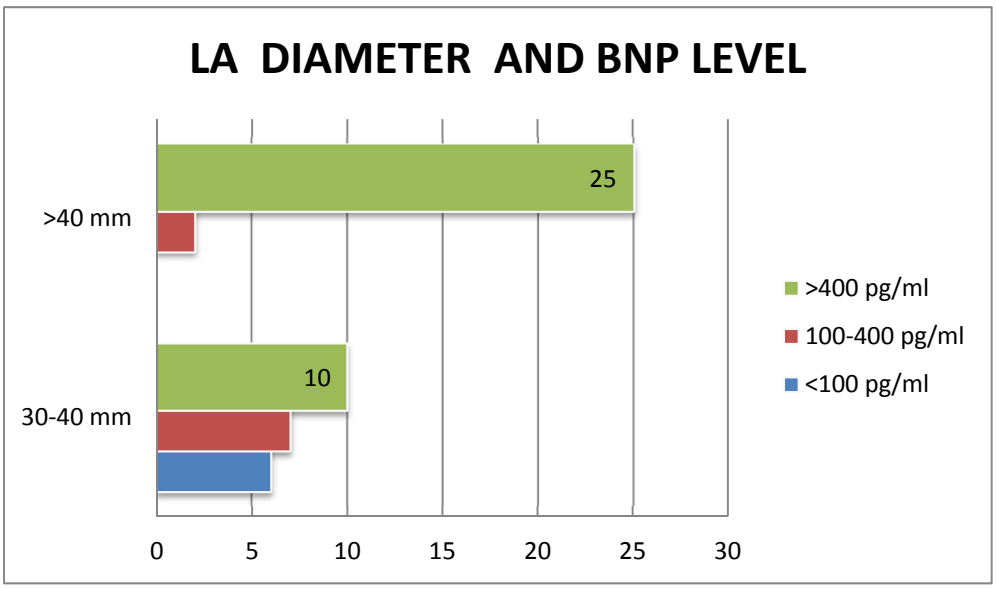


FIG : 31 – Impact of Left Atrial Diameter on BNP value

From this analysis it is suggested that mean LA diameter was prominent in majority of the patients i.e. 54% as >40 mm of Left atrium size followed by 46% with normal range which is 30-40 mm.

In LA enlarged patients 2 cases (7%), 25(93%) were having BNP value 100-400 pg/ml, >400 pg/ml respectively.

In normal LA patients 6 case (26%), 7 (30%), 10 (44%) were having BNP value <100 pg/ml, 100-400 pg/ml, >400 pg/ml respectively.

The value is statistically significant (p value – 0.001)

TABLE - 16

DOPPLER ECHOCARDIOGRAPHIC VARIABLES OF 50 CASES

DOPPLER VARIABLES	MEAN ± SD
E Velocity	1.02 ± 0.23 m/s
A Velocity	0.85 ± 0.27 m/s
E/A Ratio	1.29 ± 0.54
E/e' Ratio	15.49 ± 6.1

E= EARLY FILLING, A= ATRIAL FILLING, e'=EARLY DIASTOLIC VELOCITY

As seen from the above table Doppler echocardiographic variables for diastolic function mean early filling velocity (E) value was 1.02 ± 0.23 m/s, mean atrial filling (A) velocity value was 0.85 ± 0.27 m/s, mean E/A ratio was 1.29 ± 0.54, with a mean (E/e') ratio was 15.49 ± 6.1 which suggested that left ventricular end diastolic pressure was raised.

TABLE- 17

RELEVANCE OF BNP WITH E/A RATIO IN PATIENTS WITH HFPEF

E/A	<100 pg/ml	100-400 pg/ml	>400 pg/ml	Grand Total
<1	3 (16%)	5 (26%)	11(58%)	19
>1	3 (10%)	4 (13%)	24 (77%)	31
Grand Total	**6 (12%)**	**9 (18%)**	**35 (70%)**	**50**

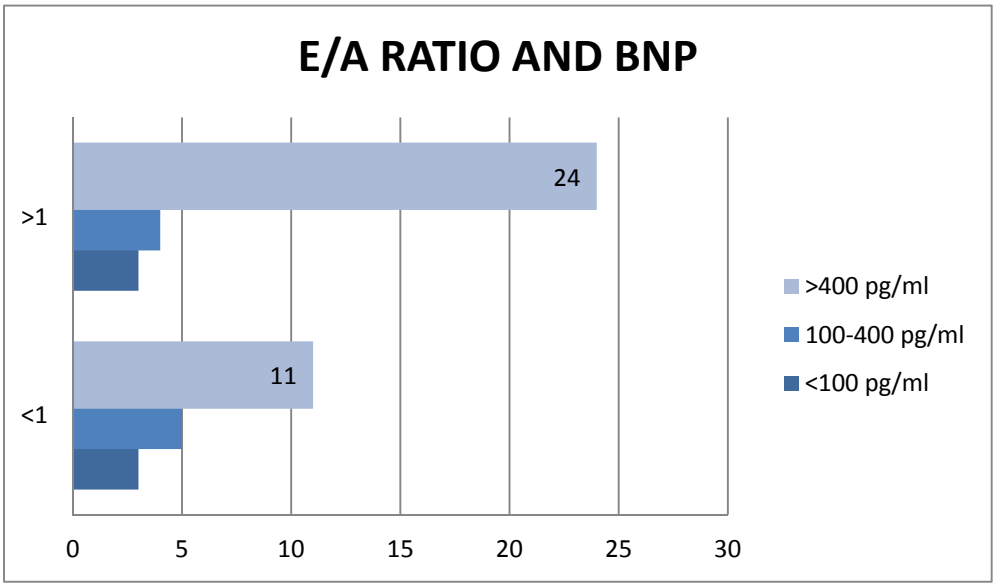


FIG : 32 – Correlation of E/A ratio with BNP value

Most of the patients were having E/A ratio >1 that is 62% followed by 38% which was E/A <1.

3 cases (10%) , 4 (13%) , 24 (77%) were having BNP value <100 pg/ml, 100-400 pg/ml, >400 pg/ml respectively with E/A ratio >1.

3 cases (16%) , 5 (26%) , 11 (58%) were having BNP value <100 pg/ml, 100-400 pg/ml, >400 pg/ml respectively with E/A ratio <1.

TABLE - 18

RELEVANCE OF BNP WITH DIASTOLIC DYSFUNCTION TYPE IN PATIENTS WITH HFPEF

Diastolic Dysfunction Type	<100 pg/ml	100-400 pg/ml	>400 pg/ml	Grand Total
DD Type 1	5 (22%)	7 (30%)	11 (48%)	23
DD Type 2	1 (8%)	1 (8%)	10 (84%)	12
DD Type 3		1(7%)	14 (93%)	15
Grand Total	**6 (12%)**	**9 (18%)**	**35 (70%)**	**50**

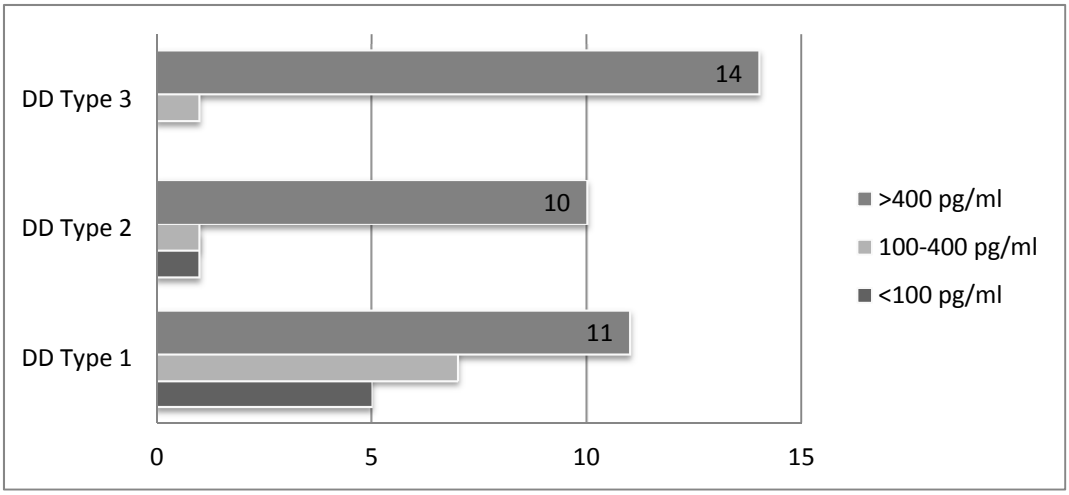


FIG : 33- Impact of DD type on BNP value.

Most of the patients were having Diastolic Dysfuction type 1, that is 23 cases (46%) followed by DD type 3 were 15 (30%) and then DD type 2 were 12(24%) .

In DD type 1- 5 cases(22%), 7(30%), 11(48%)were having BNP value <100 pg/ml, 100-400 pg/ml, >400 pg/ml respectively.

In DD type 2- 1 case (8%), 1(8%), 10(84%)were having BNP value <100 pg/ml, 100-400 pg/ml, >400 pg/ml respectively

In DD type 3- 1 case (7%), 14 (93%) were having BNP value 100-400 pg/ml, >400 pg/ml respectively.

The value is statistically significant (p value – 0.033)

DISCUSSION

Heart failure with preserved ejection fraction (HFPEF) is associated with substantial morbidity and mortality. Existing data suggests that the patients with HFPEF are increasing over time and hospitalization rates, death rates are approaching the patients with heart failure with reduced ejection fraction.

To know correct identification of patients with HFPEF and to differentiate between cardiac patients and dyspnoea due to non-cardiac causes studies should be done to know the proper diagnostic guidelines for HFPEF. In our study, relevance of BNP in heart failure with LVEF ≥ 50% and absence of left ventricular dilation (LVIDd ≤ 55 mm) on echo examination along with Presence of symptoms and signs of Congestive Heart failure at the time of presentation and evidence of diastolic dysfunction on Doppler examination were used to diagnose heart failure with preserved ejection fraction.

The present study is an observational study of 50 patients of heart failure with preserved ejection fraction in whom baseline characteristics of the patients in terms of age & sex distribution, vital parameters, laboratory parameters, comorbities, M- mode echocardiography , NYHA class, Diastolic dysfunction type at the time of presentation, and correlation of various parameters and echocardiographic variables with BNP were studied.

AGE AND BNP IN HFPEF

The mean age of our patients was 63.06 years and majority were in group of 61-70 years of age that is 34 %. In Devereux et al[69] showing mean age of 64 years,

MacCarthy et al showing mean age of 63 years, This observation can be attributable as HFPEF is more common in elderly age group.

In our study, we found out that BNP values are closely associated with age. As the age increases BNP value tends to increase. In Kayzer JM et al analysis of variance demonstrated that BNP data were significantly dependent on age ($p<0.001$)[107]

Mottram PM et al studied that in patients with HF with normal ejection fraction, BNP is related to Age and blood pressure.[108]

GENDER AND BNP IN HFPEF

Along with age in present study HFPEF was more common in female with female to male ratio of 1.6:1. Present study observed that 62% patients of HFPEF were females which suggesting that diastolic dysfunction is more commonly seen in females which is consistent to other studies i.e. Devereux et al [69] showing 84% of females, Lee et al [66] showing 65% of females and Bursi et al[67] showing 57 % of females.

As seen from our study, there were 62 % females with 38 % males and showed females having more BNP value as compared to males suggesting that gender having direct correlation with BNP value. Roongsritong C et al study showed BNP was significant and he found out that BNP values are higher in women with diastolic dysfunction than males($p=0.002$).[109] Kayzer et al found out that that BNP data were significantly dependent on gender ($p=0.002$).[107]

BMI AND BNP

In present study majority of our patients were overweight (56%) with BMI of 23-27.4 kg/m^2 and had elevated BNP leves as in other studies like in Lee et al[66] study mean BMI was 27kg/$m^{2,}$, in Devereux et al[69] was 33.1 kg/m2 and Bursi et al[67] mean BMI was 30kg/m2. This difference in mean can be attributed to the ethnicity and baseline difference in height and weight of the patients. In present study we observed that only 12% of the patient with high BMI showed BNP in normal range.

VARIOUS COMORBID CONDITIONS IN HFPEF

The present study showed that 68 % of patients were hypertensive, 62% were diabetic, 26% were anaemic, 26% were having hyperlidaemia, 6 % had AF, 6% had hypothyroidism. This observation was comparable to Lee et al [66] which had 59% patients as hypertensive, 22 % as diabetic, 29 % having atrial fibrillation and 59 % showed hyperlipidaemia. Bursi et al [67] study showed that 86 % patients as hypertensive, 36 % as diabetic and 31 % having atrial fibrillation.

HYPERTENSION AND BNP

It has been seen that HFPEF is more commonly seen in patients having hypertension. In present study it was found that 68 % were hypertensive and a mean systolic BP was 167.8 mm Hg & mean diastolic was 103.8 mm Hg and had higher BNP values as compared to non hypertensive patients. Our study is statistical significant (p – 0.019)

Lee et al[66], Devereux et al[69] , it was found that baseline mean blood pressure was high in 59 %,and 76 % respectively.

Mottram PM et al studied that in hypertensive patients with symptoms suggestive of HF with normal ejection fraction, BNP is related to Hypertension with atrial and ventricular systolic parameters.[108]

This observation is because of the underlying pathophysiology of HFPEF due to hypertension causing the pressure overload leading to left ventricular hypertrophy and fibrosis and leading to diastolic dysfunction. It has been seen that isolated systolic hypertension in patients with heart failure causes concentric hypertrophy in females and eccentric hypertrophy in males and this could be the one reason that could contribute to increased risk of diastolic dysfunction more in women than males. Furthermore, hypertension causes increased left atrial pressure and resulting in pulmonary venous hypertension and increased signs and symptoms of heart failure. Physical examination can also reveal signs of hypertension by loud A2, laterally displaced cardiac impulse.

DM AND BNP

In our study 31 patients out of 50 were diabetic (62 %) and showed directly relation with BNP values as there is higher values in diabetic patients. Our study is statistical significant (0.001).

Dal k et al study showed High BNP levels were directly correlated with HbA1C and FBS values.[110] This showed that diabetic patients are more prone for getting diastolic dysfunction as compared to normal individual and directly linked with BNP value.

ANAEMIA AND BNP

In our study, Most of the patients were non anaemic but patients with low Hb levels had high BNP value. As in females 8 patients were anaemic out of which 5 patients had BNP value more than 400 pg/ml and in males 5 cases were anemic all showed high BNP value with more than 400 pg/ml.

Hirofumi Ueno et al[82] studied the correlation between anaemia, BNP and the outcome in 185 patients with heart failure and found that synergistic effect of anaemia combined with high BNP levels significantly predicts an enhanced risk for major adverse cardiac events. In other study by Wu AH et al[83] which studied the relationship of anaemia and BNP in patients with and without heart failure and it was found that incidence of anaemia was higher in patients with heart failure (48% v/s 32%) with a higher mean BNP value (439 pg/ml v/s 35pg/ml).

ECHOCARDIOGRAPHIC VARIABLES IN HFPEF

M mode echocardiography variables of our 50 patients were studied. The various parameters included LA size, LVIDd, LVIDs and LVEF. Mean LA size was enlarged in all the patients with mean size of 39.86 mm. In a study done by Omar Issa et al[71] studied the correlation of LA size in HFPEF and founded that mean LA size was enlarged in all patients with HFPEF with a mean of 40.2 mm. In another study by Angela B. S. Santos et al[111] studied the LA function by strain analysis using speckle tracking as a direct measure of intrinsic LA myocardial deformation in 357 patients in HFPEF and found that mean LA size was enlarged. This could be due to the alteration of LV diastolic function leading to reduced LV recoil and suction during diastole. As a result, these patients are more dependent on atrial pump function in late diastole to

maintain normal ventricular filling i.e. more afterload and more chamber tension and with progressive elevation of LV filling pressure there will be remodelling and this compensatory mechanism will gradually impair resulting in elevated left atrial pressure. Patients with enlarged LA size hospitalized more as compared to normal size. Recent studies are showing that patients with HFPEF had increased left atrial contribution to LV filling as a compensatory response to impaired early LV filling during submaximal exercise and these patients have more exercise related symptoms and as the disease progresses left atrial function failed to increase, resulting in insufficient compensation during late diastolic filling and heart failure progresses and symptoms suddenly aggravates.

We also studied Doppler echo parameters namely E velocity, A velocity, E/A ratio, e' velocity and E/e' ratio.Zile et al found E/A ratio of 1.05 ± 0.74, E/e' at lateral annulus of 10 ± 4.5 at baseline in 745 patients. The results of these studies are consistent with our findings.

NYHA AND BNP

In our study majority of the patients of heart failure with preserved ejection fraction had NYHA Class III (58 %) followed by class IV (42 %), which suggests that patients were in failure at the time of presentation. Most of the patients in grade III and IV of NYHA class having higher BNP suggesting its direct correlation with NYHA class as Higher NYHA Class showed higher BNP Values. The value is statistically significant (p value – 0.049)

Wu ah et al [83] showed in patients with heart failure with a higher mean BNP value had NYHA class III and IV.

DIASTOLIC DYSFUNCTION AND BNP

Regarding diastolic dysfunction we had 23 patients with baseline diastolic dysfunction grade I. 12 patients with diastolic dysfunction with grade II. 15 patients was in diastolic dysfunction with grade III.

Edelmann et[79] al also graded diastolic dysfunction at baseline. Majority of the patients had diastolic dysfunction grade I which was consistent with our findings and also he checked diastolic dysfunction at 12 months after giving treatment with spironolactone and 98 % of the patients continued to have same type of grades even though after controlling hypertension.

In our study, higher the dystolic dysfunction, level of BNP is also higher and Diastolic Dysfunction Type 3 showed elevated BNP values compared to Type 1 and 2 which is statistically significant(p- 0.0333) as Scardovi AB et al study showed B-type natriuretic peptide was higher in patients with severe diastolic dysfunction than in those without(459±462pg/mL vs 142±166pg/mL,) [112] .This study was significant (p <0.001).

LEFT ATRIAL DIAMETER IN HFPEF AND BNP

We also studied the correlation of LA diameter with BNP and found that more the LA diameter more is the BNP values which was supported by Venkatesh Y. Anjan study.[74] They compared the clinical characteristics including LA size in 139 patients with BNP < 100 pg/ml and with BNP > 100 pg/ml and found that patients with large LA size had raised BNP values and patient with BNP< 100 pg/ml had normal LA size. It is concluded that BNP values correlates with the LA size. In our study which showed mean LA size was prominent in majority of the patients i.e. 54% as >40 mm

of Left atrium size followed by 46% with normal range which is 30-40 mm. In LA enlarged patients 25 cases out of 27 were having BNP value >400 pg/ml. Our study is statistically significant (p value- 0.001).

SUMMARY

Heart failure with preserved ejection fraction (HFPEF) contributes about 40-50 % of total cases of heart failure. The present study of 50 cases of HFPEF was aimed at highlighting the relevance of Brain natriuretic peptide in various parameters of HFPEF along with importance of Doppler echocardiographic indices of diastolic dysfunction and associated comorbities which are commonly associated with this type of heart failure.

- All the 50 patients of HFPEF were taken on the basis of heart failure symptoms according to Framingham's criteria, Doppler echo indices of diastolic dysfunction EF of ≥ 50 %, absence of Left ventricular dilation.
- In the present study, out of 50 cases of HFPEF, maximum number of the cases was in the age group of 61-70 years of age and majority of them were females . This study shows that elevated BNP is seen more commonly in elderly women.
- Majority of the patients were hypertensive and diabetic in our study.
- Out of the 50 cases majority were overweight/obese as per their BMI indices .This study implying obesity constitutes an important risk factor in development of HFPEF and directly associated with BNP .
- Most of the cases had some associated comorbities like anaemia, dyslipidaemias, Hypothyroidism, Atrial fibrillation, OSA and demonstrates correlation with HFPEF and BNP and should be treated simultaneously to decease the overall mortality .

- Most of the patients in grade III and IV of NYHA class having higher BNP suggesting its direct correlation with NYHA class as Higher NYHA Class showed higher BNP Values.
- As the DD severity aggravated, the percentage of higher BNP also increased which showed BNP values directly dependent on Diastolic Dysfunction Type.
- On Doppler echocardiographic variables mean LA Diameter was increased in most of the patients. There is significant correlation between LA size and BNP levels implying that BNP levels increases as the LA size increases which can be an indirect measure for diastolic dysfunction and can guide regarding the monitoring of the treatment .
- The result obtained from this study is comparable with international studies showing the association of BNP with various parameters and HEPEF.

CONCLUSION

To conclude that HFPEF is a major and growing health problem and has become a huge economic burden and representing half of all patients with heart failure. Despite improvement in understanding of the disease, the challenge lies in diagnosis of these cases to start early management.

Advancement in the diagnostic algorithm, imaging and blood test BNP will allow early diagnosis so that treatment may be implemented early in the disease progression. All these patients can be benefited from blood pressure control, heart failure education (DASH diet, Exercising, Yoga), Diabetic management and diagnosing and treating the other comorbities like anemia, obesity which can be the leading causes of HFPEF.

Serum BNP can be used as a marker for the correlation in which diagnosis is not clear .However the awareness of this condition and associated factors is necessary to manage this condition. In this study it was seen that hypertension, diabetes mellitus, Left atrial diameter were commonly associated with HFPEF and BNP. Other comorbidities like AF, obesity, dyslipidemia, atrial fibrillation were also seen..

So Serum BNP levels helps in stratifying patients for prognosticating but further studies are required to identify patients who may get benefit from close surveillance and tighter control of their risk factors.

LIMITATIONS OF THE STUDY

- The study was conducted at a medical college hospital which is a tertiary care centre and the demographic data of the cases studied may not be a representative sample of the whole population or a particular region.
- The short duration of study and the small number of cases in comparison to the disease burden are the limitations of this study

RECOMMENDATIONS OF THE STUDY

- We recommend that further studies can be done on a larger scale in a population based setting
- It is not enough to only study the prevalence but we need to evaluate the treatment modalities which was not done in this study.

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INSTITUTIONAL HUMAN ETHICS COMMITTEE

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES,
KULASEKHARAM, TAMILNADU

Communication of Decision of the Institutional Human Ethics Committee(IHEC)

SMIMS/IHEC No: 1 /Protocol no: 40 / 2016

Protocol title: RELEVANCE OF SERUM BNP LEVEL IN THE STUDY OF HEART FAILURE WITH PRESERVED EJECTION FRACTION AT TERTIARY HOSPITAL
Principal Investigator: Dr. Ankush Gupta
Name& Address of Institution: Department of General Medicine Sree Mookambika Institute of Medical Sciences, Kulasekharam ☑ New review ☐ Revised review ☐ Expedited review
Date of review (D/M/Y): 15-12-2016 Date of previous review , if revised application:
Decision of the IHEC: ☑ Recommended ☐ Recommended with suggestions ☐ Revision ☐ Rejected
Suggestions/ Reasons/ Remarks:
Recommended for a period of : eighteen months

Please note*

- Inform IHEC immediately in case of any Adverse events and Serious adverse events.
- Inform IHEC in case of any change of study procedure, site and investigator
- This permission is only for period mentioned above. Annual report to be submitted to IHEC.
- Members of IHEC have right to monitor the trial with prior intimation.

Signature of Member Secretary IHEC

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES ★ KULASEKHARAM ★
IHEC
Date 21/12/16

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES

KULASEKHARAM

RESEARCH COMMITTEE

CERTIFICATE

This is to certify that The Research Protocol Submitted by DR. ANKUSH GUPTA

Faculty / Post Graduate from Department of GENERAL MEDICINE

Titled To Study heart failure c preserved ejection fraction based on NYHA classification, Transthoracic Echocardiography & Serum BNP level at tertiary hospital.

is approved by the Research Committee.

Chair Person

Prof. & H.O.D.
Dept. of Bio-Chemistry
Sree Mookambika Institute of Medical Sciences
Kulasekharam 629 161

Convenor

Prof. & H.O.D.
Dept. of Physiology
Sree Mookambika Institute of Medical Sciences
Kulasekharam 629 161

Date :

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES
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DEPARTMENT OF GENERAL MEDICINE

RELEVANCE OF SERUM BNP LEVEL IN THE STUDY OF HEART FAILURE WITH PRESERVED EJECTION FRACTION AT TERTIARY CARE HOSPITAL

CASE RECORD FORM

OPD/IPD No. : **Date:**

Age: **Gender:**

Marital Status: **Occupation:**

Address: **Chief Complaints:**

Past History

- DM - Yes ~ No ~
- HTN - Yes ~ No ~
- TB - Yes ~ No ~
- MI - Yes ~ No ~
- Stroke - Yes ~ No ~
- Renal Dysfunction - Yes ~ No ~
- Liver Disease - Yes ~ No ~
- COPD - Yes ~ No ~

Family History:

General Examination

1) Pallor Present/ Absent
2) Pedal Edema Present/ Absent
3) Icterus Present/ Absent
4) Cyanosis Present/ Absent
5) Clubbing Present/ Absent
6) Lymphadenopathy Present/ Absent
7) Pedal edema Present/ Absent
8) JVP Present/ Absent

Height : …….. cm Wt : …….kg BMI …….kg/m ^{2}

Pulse: ……..bpm BP: ……...mmhg

Framingham Criteria for Congestive Heart Failure

Diagnosis of CHF requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria.

Major criteria:

- Paroxysmal nocturnal dyspnea Yes ~ No ~
- Neck vein distention Yes ~ No ~
- Rales Yes ~ No ~
- Radiographic cardiomegaly Yes ~ No ~
  - Acute pulmonary edema Yes ~ No ~
  - S3 gallop Yes ~ No ~
  - Hepatojugular reflux Yes ~ No ~
  - Weight loss >4.5 kg in 5 days in response to treatment Yes ~ No ~

Minor criteria:

- Bilateral ankle edema Yes ~ No ~
- Nocturnal cough Yes ~ No ~
- Dyspnea on ordinary exertion Yes ~ No ~
- Hepatomegaly Yes ~ No ~
- Pleural effusion Yes ~ No ~
- Tachycardia (heart rate>120 beats/min.) Yes ~ No ~

BASE LINE INVESTIGATION

- Hb :
- TLC :
- DLC :
- RBS :
- RFT :
- LIPID PROFILE:
- LFT:
- BNP :
- ECG:

Urine

i) R:

ii) M:

Echo Parameters

- LA (mm)
- LVID (ed)
- IVS (ed)
- EF(%)
- E/A ratio
- MVDT

- LV PW (ed)
- RWMA

Pericardial Effusion/Disease:

Diastolic dysfunction grade: ……

Grade I (Impaired relaxation with normal filling pressure.)

Grade II (moderate dysfunction, pseudonormalised mitral inflow pattern)

Grade III severe reversible, reversible restrictive (High Filling Pressure)

Grade IV (severe irreversible dysfunction irreversible restrictive pattern (High Filling Pressure)

INFORMED CONSENT DOCUMENT (ICD)
PATIENT/PARTICIPANT INFORMATION SHEET
INFORMATION FOR PARTICIPANTS OF THE STUDY

1. Title of the Study:- Relevance of Serum BNP Level in the study of Heart Failure with Preserved Ejection Fraction at Tertiary Care Hospital

2. Name of the investigator : Dr. Ankush Gupta
Postgraduate – MD General Medicine
Sree Mookambika Institute of Medical Sciences
Kulasekharam
Mobile: 8529588758
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Name of the Guide : Dr. J. Kaniraj Peter
Professor and HOD
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Name of co-guide : Dr Ajay Kumar
Chief Cardiologist and Assistant Professor
Department of Cardiology
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Mobile : 9446565626
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3. Purpose of this project/study: Diastolic dysfunction is difficult to differentiate from systolic dysfunction on the basis if history, physical examination, and electrocardiographic and chest radiographic findings. Therefore objective testing with Doppler echocardiography and possibly measurements of serum levels of Brain-Type

natriuretic peptide (BNP) is often required. BNP and N Terminal-Pro BNP levels are found to be related to the severity of left diastolic dysfunction.

The treatment of diastolic heart failure is also less well defined then the treatment of systolic heart failure and remains a challenge. Hence the need for study. It is planned to study all such cases of heart failure with normal ejection fraction (HFNEF) in detail by ECHO and raised brain type natriuretic peptide (BNP) levels. This study may help us understand the characteristic of this disorder.

4. Procedure/ methods of the study:

All eligible patients will be enrolled, written and informed consent will be obtained from them. Apart from demographic details, detailed history will be taken and physical examination, routine and blood investigation will be done and suspected heart failure patients will go through Transthoracic echocardiography and BNP testing to diagnose the heart failure with preserved ejection fraction and will classified acc to diagnostic dysfunction.

5. Expected duration of the subject participation:- Single visit

6. The benefits to be expected from the research to the participant: To decrease the Mortality and morbidity rate among heart failure patients.

7. Any risk expected from the study to the participant:- Nil

8. Maintenance of confidentiality of records:- All data collected for the study will be kept confidentially. No personal details will be revealed.

9. Provision of free treatment for research related injury:- Yes

10. Compensation for participating in the study:- No

11. Compensation to the participants for forseable risks and unforeseeable risks related to research study leading to disability or death:- No

12. Freedom to withdraw from the study at any time during the study period without the loss of benefits that the participant would otherwise be entitled:- Yes

13. **Possible current and future uses of the biological material and of the data to be generated from the research and if the material is likely to be used for secondary purposes, or would be shared with others, this should be mentioned:-** N/A

14. **Whom do I contact for further information:**

For any study related queries, you are free to contact

Dr. Ankush Gupta
Post Graduate – MD General Medicine
Department of General Medicine
Sree Mookambika Institute of Medical Sciences, Kulasekharam
Mobile number: 08529588758
e-mail: dr.guptankush@gmail.com

Place: Kulasekharam

Date:

Signature of Participant

CONSENT FORM

TITLE OF THE PROJECT:- Relevance of Serum BNP Level in the study of Heart Failure with Preserved Ejection Fraction at Tertiary Care Hospital

PARTICIPANTS NAME:

ADDRESS:

The details of the study have been provided to me in writing and explained to me in my own language. I confirm that I understood the above study and had the opportunity to ask questions, I understand that my participation in this study is voluntary and that I am free to withdraw at any time. Withdraw at any time, without giving any reason, without the medical care that will be normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose. I have been given an information sheet giving details of this study. I fully consent to participate in the above study.

(I also consent/ do not consent to use my stored biological samples for future scientific purposes: Yes/No – if Applicable)

Signature of the Participant: _____Date:_____

Signature of Witness:_____Date:_____

Name and Address of Witness:

Signature of the Investigator:_____Date: _____

S.NO.	AGE	SEX	HT(CM)	WT(KG)	COMORBITIES	BMI(KGM2)	BP		PULSE	HB	TLC	RBS	UREA	CREAT	T.CHOL	S.BIL	BNP	NYHA CLASS	LA	AO	LVID(d)	LVID(es)	EF	E(m/s)	A(m/s)	E/A	E/e'	DD TYPE
							SYST.	DIAS.																				
1	75	M	165	74	HTN/COPD/AF	27.2	160	100	100	16	7700	186	36	1.1	230	0.8	2012	IV	41	32	34	28	60	0.94	1.25	0.75	12	1
2	67	M	170	71	HTN/AF	24.5	200	100	116	13	10500	191	46	1	210	0.4	670	III	36	29	27	30	52	1.35	0.54	1.4	18	1
3	87	M	180	72	CVA/HTN/AF	22.2	150	100	78	14	8500	109	22	0.8	149	0.5	18000	III	45	25	32	25	62	1.35	0.58	2.3	30	2
4	93	F	158	60	HTN	24	150	90	102	13	9800	224	32	0.9	148	0.6	2239	IV	42	28	50	22	62	1.06	0.5	2.1	22	1
5	60	F	160	70	HTN	27.3	150	100	82	15	12300	100	22	0.8	229	0.6	2090	III	42	30	45	30	58	1.02	0.6	1.7	18	1
6	40	F	162	70	x	26.7	110	70	120	13	7600	128	26	0.8	180	0.4	98	III	38	33	52	23	64	1.1	0.88	1.3	10	1
7	50	M	170	82	HTN/DM/CVA	28.3	180	110	100	11	8200	161	29	0.4	143	0.9	498	III	53	31	52	29	60	1.07	0.7	1.5	9	1
8	56	F	160	70	x	27.3	120	70	100	14	20000	100	25	1.1	180	0.2	367	III	34	26	38	26	52	0.98	0.68	1.02	13	1
9	70	M	166	78	HTN/COPD	28.3	210	170	86	13	6000	160	29	1	193	0.7	481	III	23	23	31	20	55	0.96	0.68	1.4	13	1
10	62	F	162	65	HTN/DM/CKD	24.7	150	90	88	12	20000	100	98	3.7	160	0.3	4047	IV	44	22	45	23	60	1.21	0.84	1.4	25	3
11	65	F	165	60	x	22	120	84	98	12	5600	112	26	0.3	150	0.2	220	III	39	26	43	22	60	0.63	0.84	0.75	12	1
12	55	F	180	80	HTN/AF	24.7	140	90	90	12	11400	120	36	1.2	168	6.9	8998	IV	41	26	40	23	60	1.2	0.9	1.33	19	2
13	80	F	158	56	HTN/DM	22.4	170	100	108	14	14500	102	30	1.2	188	0.8	2849	IV	41	28	30	26	64	1.06	0.5	2.1	20	1
14	63	M	154	58	DM	24.5	100	60	90	15	8600	100	23	0.7	140	2.9	1094	IV	51	27	50	37	62	1.3	0.62	2	12	1
15	42	M	172	65	HTN/DM	22	180	100	90	15	8300	248	27	0.6	200	0.4	4998	IV	42	27	46	33	55	1.28	0.94	1.36	22	1
16	40	M	180	78	x	24.1	100	70	98	12	8000	168	28	1.2	180	0.2	210	III	40	23	42	31	55	0.79	1.09	0.7	14	1
17	65	F	168	66	HTN/CVA/DM	23.4	170	100	76	14	4500	113	27	1.2	772	0.8	1098	IV	45	25	41	28	62	1.41	0.71	2.1	14	3
18	40	M	174	68	HTN/DM	22.4	170	100	76	13	4500	110	27	1.1	240	1.3	584	III	37	33	31	20	55	1.45	0.62	2.3	28	2
19	65	F	168	68	HTN/DM	24	170	120	84	13	14900	407	32	1.2	250	6.2	>2500	IV	42	26	41	35	55	1	0.88	1.1	30	1
20	60	F	154	54	HYPOTHYROIDISM	22.7	130	80	80	11	12300	120	14	1.2	130	0.5	70	III	28	26	52	23	60	0.94	1.25	0.75	12	2
21	58	M	172	72	COPD/HTN/CKD/DM	24.3	160	100	100	12	11500	128	101	4.8	210	0.5	1980	IV	42	26	42	23	60	1.06	0.5	2.1	21	3
22	60	M	168	70	HTN/DM/COPD/	24.8	180	110	102	12	10000	348	33	1.07	260	0.2	2372	IV	41	31	50	16	60	1.06	0.62	1.7	20	2
23	60	F	150	55	HTN/DM	24.4	170	100	86	14	8200	120	32	0.9	180	0.2	475	III	40	21	20	20	60	0.96	0.68	1.4	12	1
24	45	M	155	80	OSA/DM	33.3	130	70	86	9.1	10500	92	24	1.2	210	0.7	1288	IV	30	28	45	20	60	1.21	0.84	1.4	24	3
25	65	F	165	60	x	22	120	80	86	12	14500	100	31	0.8	180	0.8	80	III	27	32	43	24	55	1.06	0.5	2.1	22	1
26	50	F	154	61	DM	25.7	130	90	86	12	10000	554	29	0.8	190	0.2	6.8	III	30	32	42	25	60	1.36	0.72	0.5	12	3
27	42	M	170	90	X	31.1	120	70	108	13	22000	150	38	0.3	193	0.8	280	III	43	33	50	31	55	0.84	1.4	0.6	8	2
28	56	M	175	95	HTN/T2DM	31	150	90	90	12	6800	250	25	1.2	180	0.2	442	III	40	24	36	22	58	0.87	0.96	0.9	16	1
29	60	F	154	62	DM	26.1	130	80	100	10	63	96	32	1.1	150	1.4	6523	III	43	21	38	26	60	1.21	0.84	1.4	24	2
30	65	F	160	58	HTN/T2DM	22.6	150	90	110	12	9000	298	18	1	218	0.2	1299	IV	40	28	50	39	60	1.06	1.12	0.9	22	3
31	60	F	156	55	HTN/T2DM	23.8	150	96	110	9.2	14500	132	26	1.1	180	0.4	83	III	40	25	46	29	60	0.62	1.08	0.5	10	3
32	80	F	156	56	HTN/DM	22.6	140	94	104	10	10000	147	24	0.7	146	0.2	1227	IV	43	28	55	34	55	0.94	1.25	0.75	12	2
33	62	F	160	80	HTN/T2DM	31.2	160	100	100	12	12500	240	30	1	230	0.6	778	III	42	26	48	30	60	0.84	1.4	0.6	8	3
34	58	M	170	85	HTN	29.4	150	90	90	8.2	6900	171	30	0.8	193	0.7	70	III	24	20	36	32	60	1.3	0.68	1.9	15	1
35	62	F	162	62	HTN/DM	23.6	160	100	98	12	5700	120	35	0.8	180	0.2	790	IV	42	30	45	32	60	1.3	0.68	1.9	15	2
36	78	F	160	63	DM2	24.6	110	70	96	13	9000	128	37	1	160	0.5	920	III	42	28	44	28	60	0.86	1.12	0.76	10	3
37	68	F	158	64	HTN/DM/HYPOTHYROIDISM	25.6	170	110	90	11	7800	186	32	0.6	190	1.1	1500	IV	40	25	45	30	60	0.74	1.32	0.6	14	1
38	52	M	170	80	HTN/T2DM	27.7	150	90	100	16	800	190	26	1.2	140	0.5	1020	III	42	25	45	30	58	0.82	0.82	1.4	12	3
39	65	F	160	66	HTN/DM	25.8	160	100	86	13	7200	160	32	1.2	180	0.2	7720	IV	44	22	38	28	60	1.21	1.21	1.4	22	3
40	60	F	165	68	HTN/T2DM	25	170	100	92	13	8200	396	26	1.2	210	0.8	1612	III	45	28	47	32	55	0.75	0.93	1.16	14	1
41	70	F	156	58	HTN	23.8	140	100	98	9.2	9000	110	32	0.5	150	0.2	620	III	40	26	50	34	54	0.94	1.25	0.75	11	2
42	60	F	160	72	HYPOTHYROIDISM	28.1	120	80	100	10	7900	160	39	0.7	180	0.4	220	IV	40	28	46	34	60	0.58	1.08	0.53	10	3
43	76	F	162	65	HTN/T2DM	24.7	160	100	98	11	7800	280	18	0.6	200	0.3	910	III	44	28	48	24	60	0.74	0.82	0.9	12	1

S.NO.	AGE	SEX	HT(CM)	WT(KG)	COMORBITIES	BMI(KGM2)	BP		PULSE	HB	TLC	RBS	UREA	CREAT	T.CHOL	S.BIL	BNP	NYHA CLASS	LA	AO	LVID(d)	LVID(es)	EF	E(m/s)	A(m/s)	E/A	E/e'	DD TYPE
							SYST.	DIAS.																				
44	70	M	165	72	HTN/DM	26.4	180	100	90	12	6000	80	58	1.2	120	0.6	460	III	50	50	50	36	58	1.07	1.2	1	2	2
45	65	F	168	68	HTN	24	168	100	94	13	6700	140	30	0.5	160	0.3	305	III	38	28	46	32	60	0.84	0.7	1.2	15	3
46	80	F	160	62	COPD/HTN	24.2	170	90	100	11	8000	120	34	0.6	190	0.3	250	III	42	30	40	28	58	0.96	0.6	1.6	13	1
47	65	M	176	82	HTN	26.4	170	110	100	13	5700	124	40	1	188	0.4	350	IV	40	21	40	22	60	0.45	0.5	0.9	12	3
48	80	M	170	70	HTN/DM	24.2	150	90	90	13	5600	195	33	1.1	120	1.2	291	IV	40	24	48	30	60	1.02	0.5	1.9	11	3
49	85	F	160	58	DM	22.6	110	80	90	11	6200	100	28	1.1	170	0.2	450	IV	42	30	46	31	60	1.2	0.62	1.9	12	2
50	85	F	160	52	DM	20.3	120	70	90	15	9000	122	40	0.7	228	0.3	430	III	40	28	35	21	60	0.63	0.74	0.7	11	1